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Boehringer Ingelheim Pharma KG

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Provisional text

New amide compounds having MCH-antagonistic activity and medicaments comprising these compounds

The present invention relates to new amide compounds, the physiologically acceptable salts thereof as well as their use as MCH antagonists and their use in preparing a pharmaceutical preparation which is suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. The invention further relates to such medicaments and a process for preparing them.

Background to the Invention

The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted obesity in recent decades. In affected people, obesity leads directly to restricted mobility and a reduction in the quality of life. There is the additional factor that obesity often leads to other diseases such as, for example, diabetes, dyslipidaemia, high blood pressure, arteriosclerosis and coronary heart disease. Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

The term obesity means an excess of adipose tissue. In this connection, obesity is fundamentally to be seen as the increased level of fatness which leads to a health risk. In the last analysis it is not precisely possible to draw a distinction between normal individuals and those suffering from obesity, but the health risk accompanying obesity is presumed to rise continuously as the

level of fatness increases. For simplicity's sake, in the present invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30 are preferably regarded as suffering from obesity.

Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity. One approach which has been proposed very recently is the therapeutic use of MCH antagonists (cf. *inter alia* WO 01/21577, WO 01/82925).

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids. It is synthesised predominantly in the hypothalamus in mammals and from there travels to other parts of the brain by the projections of hypothalamic neurones. Its biological activity is mediated in humans through two different glycoprotein-coupled receptors (GPCRs) from the family of rhodopsin-related GPCRs, namely the MCH receptors 1 and 2 (MCH-1R, MCH-2R).

Investigations into the function of MCH in animal models have provided good indications for a role of the peptide in regulating the energy balance, i.e. changing metabolic activity and food intake [1,2]. For example, after intraventricular administration of MCH in rats, food intake was increased compared with control animals. Additionally, transgenic rats which produce more MCH than control animals, when given a high-fat diet, responded by gaining significantly more weight than animals without an experimentally altered MCH level. It was also found that there is a positive correlation between phases of increased desire for food and the quantity of MCH mRNA in the hypothalamus of rats. However, experiments with MCH knock-out mice are particularly important in showing the function of MCH. Loss of the

neuropeptide results in lean animals with a reduced fat mass, which take in significantly less food than control animals.

The anorectic effects of MCH are mediated in rodents through the $G_{\alpha s}$-coupled MCH-1R [3-6]. Unlike primates, ferrets and dogs, no second receptor has hitherto been found in rodents. After losing the MCH-1R, knock-out mice have a lower fat mass, an increased energy conversion and, when fed on a high fat diet, do not put on weight, compared with control animals. Another indication of the importance of the MCH-MCH-1R system in regulating the energy balance results from experiments with a receptor antagonist (SNAP-7941) [3]. In long term trials the animals treated with the antagonist lose significant amounts of weight.

In addition to its anorectic effect, the MCH-1R antagonist SNAP-7941 also achieves additional anxiolytic and antidepressant effects in behavioural experiments on rats [3]. Thus, there are clear indications that the MCH-MCH-1R system is involved not only in regulating the energy balance but also in affectivity.

Literature:

1. Qu, D., et al., *A role for melanin-concentrating hormone in the central regulation of feeding behaviour.* Nature, 1996. **380**(6571): p. 243-7.
2. Shimada, M., et al., *Mice lacking melanin-concentrating hormone are hypophagic and lean.* Nature, 1998. **396**(6712): p. 670-4.
3. Borowsky, B., et al., *Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist.* Nat Med, 2002. **8**(8): p. 825-30.
4. Chen, Y., et al., *Targeted disruption of the melanin-concentrating hormone receptor-1 results in hyperphagia and resistance to diet-induced obesity.* Endocrinology, 2002. **143**(7): p. 2469-77.
5. Marsh, D.J., et al., *Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism.* Proc Natl Acad Sci U S A, 2002. **99**(5): p. 3240-5.

6. Takekawa, S., et al., *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist.* Eur J Pharmacol, 2002. **438**(3): p. 129-35.

In the patent literature certain amine compounds are proposed as MCH antagonists. Thus, WO 01/21577 (Takeda) describes compounds of formula

$$Ar^1\text{—}X\text{—}Ar\text{—}Y\text{—}N\begin{matrix}\diagup R^1\\ \diagdown R^2\end{matrix}$$

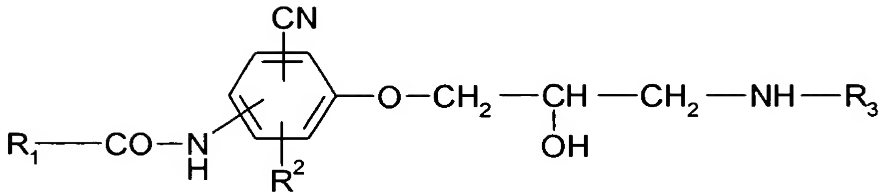
wherein Ar^1 denotes a cyclic group , X denotes a spacer, Y denotes a bond or a spacer, Ar denotes an aromatic ring which may be fused with a non-aromatic ring, R^1 and R^2 independently of one another denote H or a hydrocarbon group, while R^1 and R^2 together with the adjacent N atom may form an N-containing hetero ring and R^2 with Ar may also form a spirocyclic ring, R together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity.

Moreover WO 01/82925 (Takeda) also describes compounds of formula

$$Ar^1\text{—}X\text{—}Ar\text{—}Y\text{—}N\begin{matrix}\diagup R^1\\ \diagdown R^2\end{matrix}$$

wherein Ar^1 denotes a cyclic group , X and Y represent spacer groups, Ar denotes an optionally substituted fused polycyclic aromatic ring, R^1 and R^2 independently of one another represent H or a hydrocarbon group, while R^1 and R^2 together with the adjacent N atom may form an N-containing heterocyclic ring and R^2 together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity, *inter alia*.

In EP 073 016 A1 (Boehringer Ingelheim) 1-aryloxy-3-alkylamino-2-propanols of general formula



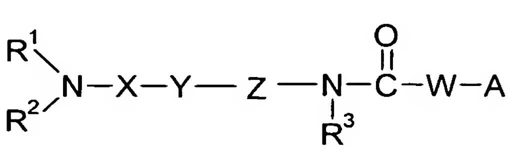
wherein R_1 may represent aryloxyalkylene, *inter alia*, are proposed for use as cardiac or coronary therapeutic agents or for lowering blood pressure. However, there is no mention of these compounds having an MCH-antagonistic activity.

Aim of the invention

The aim of the present invention is to discover new amide compounds, particularly those which have an activity as MCH antagonists. The present invention further sets out to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or otherwise causally connected to MCH. In particular, the aim of this invention is to provide pharmaceutical compositions for the treatment of metabolic disorders such as obesity and/or diabetes as well as diseases and/or disorders which are associated with obesity and diabetes. Other objectives of the present invention are concerned with demonstrating advantageous uses of the compounds according to the invention. The invention also sets out to provide a process for preparing the amide compounds according to the invention. Other aims of the present invention will be immediately apparent to the skilled man from the foregoing remarks and those that follow.

Subject matter of the invention

A first object of the present invention comprises amide compounds of general formula I



I

wherein

R^1, R^2 independently of one another denote H, a C_{1-8}-alkyl or C_{3-7}-cycloalkyl group optionally substituted by the group R^{11} or a phenyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, or

R^1 and R^2 form a C_{2-8}-alkylene bridge wherein

- one or two $-CH_2-$ groups may be replaced independently of one another by -CH=N- or -CH=CH- and/or
- one or two $-CH_2-$ groups may be replaced independently of one another by -O-, -S-, -CO-, $-C(=CH_2)-$ or $-NR^{13}-$ in such a way that heteroatoms are not directly connected to one another,

while in the above-defined alkylene bridge one or more H atoms may be replaced by R^{14}, and

while the above-defined alkylene bridge may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in such a way that the bond between the alkylene bridge and the group Cy is formed

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common, adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system,

R^3 denotes H, C_{1-6}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-4}-alkyl

X denotes a C_{1-8}-alkylene bridge wherein

- a $-CH_2-$ group may be replaced by -CH=CH- or $-C\equiv C-$ and/or

- one or two $-CH_2-$ groups may be replaced independently of one another by -O-, -S-, -(SO)-, $-(SO_2)-$, -CO- or $-NR^4-$ in such a way that in each case two O, S or N atoms or an O and an S atom are not directly connected to one another,

while the bridge X may be attached to R^1 including the N atom attached to R^1 and X forming a heterocyclic group, and

two C atoms or one C and one N atom of the alkylene bridge may be joined together by an additional C_{1-4}-alkylene bridge, and

a C atom may be substituted by R^{10} and/or one or two C atoms in each case may be substituted with one or two identical or different C_{1-6}-alkyl groups, and

W independently of one another denotes a bridge selected from among $-CR^{6a}R^{6b}-O-$, $-CR^{7a}=CR^{7c}-$, $-CR^{6a}R^{6b}-NR^8-$, $-CR^{7a}R^{7b}-CR^{7c}R^{7d}-$ and $-NR^8-CR^{6a}R^{6b}-$,

Z denotes a single bond, C_{1-4}-alkylene, wherein two adjacent C atoms may be joined together with an additional C_{1-4}-alkylene bridge,

while a C atom of the alkylene bridge may be substituted with R^{10} and/or one or two C atoms independently of one another may be substituted with one or two identical or different C_{1-6}-alkyl groups, and

Y denotes one of the meanings given for Cy,

while R^1 may be attached to Y including the group X and the N atom attached to R^1 and X , forming a heterocyclic group fused to Y, and/or

X may be attached to Y forming a carbo- or heterocyclic group fused to Y, and

A denotes one of the meanings given for Cy or

Cy denotes a carbo- or heterocyclic group selected from one of the following meanings

- a saturated 3- to 7-membered carbocyclic group,
- a unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,
- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and an O or S atom as heteroatoms,
- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

while the abovementioned 4-, 5-, 6- or 7-membered groups may be attached via two common, adjacent C atoms fused to a phenyl or pyridine ring, and

in the abovementioned 5-, 6- or 7-membered groups one or two non-adjacent $-CH_2-$ groups may be replaced independently of one another by a -CO-, $-C(=CH_2)-$, -(SO)- or $-(SO_2)-$ group, and

the abovementioned saturated 6- or 7-membered groups may also be present as bridged ring systems with an imino, (C_{1-4}-alkyl)-imino, methylene, C_{1-4}-alkyl-methylene or di-(C_{1-4}-alkyl)-methylene bridge, and

the abovementioned cyclic groups may be mono- or polysubstituted at one or more C atoms with R^{20}, in the case of a

phenyl group they may also additionally be monosubstituted with nitro, and/or one or more NH groups may be substituted with R^{21},

R^4 has one of the meanings given for R^{17},

R^{6a}, R^{6b} denotes H, C_{1-4}-alkyl or CF_3,

R^{7a}, R^{7b},
R^{7c}, R^{7d} denotes H, F, C_{1-4}-alkyl or CF_3,

R^8 denotes H, C_{1-4}-alkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl,

R^{10} denotes hydroxy, ω-hydroxy-C_{1-3}-alkyl, C_{1-4}-alkoxy, ω-(C_{1-4}-alkoxy)-C_{1-3}-alkyl, amino, C_{1-4}-alkyl-amino, di-(C_{1-4}-alkyl)-amino, cyclo-C_{3-6}-alkyleneimino, amino-C_{1-3}-alkyl, C_{1-4}-alkyl-amino-C_{1-3}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkyl, cyclo-C_{3-6}-alkyleneimino-C_{1-3}-alkyl, amino-C_{2-3}-alkoxy, C_{1-4}-alkyl-amino-C_{2-3}-alkoxy, di-(C_{1-4}-alkyl)-amino-C_{2-3}-alkoxy or cyclo-C_{3-6}-alkyleneimino-C_{2-3}-alkoxy,

R^{11} denotes C_{2-6}-alkenyl, C_{2-6}-alkynyl, R^{15}-O, R^{15}-O-CO, R^{15}-CO-O, $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO or Cy,

R^{12} has one of the meanings given for R^{20},

R^{13} has one of the meanings given for R^{17},

R^{14} denotes halogen, C_{1-6}-alkyl, R^{15}-O, R^{15}-O-CO, R^{15}-CO, R^{15}-CO-O, $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO, R^{15}-O-C_{1-3}-alkyl , R^{15}-O-CO-C_{1-3}-alkyl, R^{15}-CO-C_{1-3}-alkyl, R^{15}-CO-O-C_{1-3}-alkyl, $R^{16}R^{17}N$-C_{1-3}-alkyl, $R^{18}R^{19}N$-CO-C_{1-3}-alkyl or Cy-C_{1-3}-alkyl,

R^{15} denotes H, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, phenyl or phenyl-C_{1-3}-alkyl,

R^{16} denotes H, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, C_{4-7}-cycloalkenyl, C_{4-7}-cycloalkenyl-C_{1-3}-alkyl, ω-hydroxy-C_{2-3}-alkyl, ω-(C_{1-4}-alkoxy)-C_{2-3}-alkyl, amino-C_{2-6}-alkyl, C_{1-4}-alkyl-amino-C_{2-6}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{2-6}-alkyl or cyclo-C_{3-6}-alkyleneimino-C_{2-6}-alkyl,

R^{17} has one of the meanings given for R^{16} or denotes phenyl, phenyl-C_{1-3}-alkyl, C_{1-4}-alkylcarbonyl, hydroxycarbonyl-C_{1-3}-alkyl, C_{1-4}-alkylcarbonylamino-C_{2-3}-alkyl-, N-(C_{1-4}-alkylcarbonyl)-N-(C_{1-4}-alkyl)-amino-C_{2-3}-alkyl-, C_{1-4}-alkylsulphonyl, C_{1-4}-alkylsulphonylamino-C_{2-3}-alkyl- or N-(C_{1-4}-alkylsulphonyl)-N(-C_{1-4}-alkyl)-amino-C_{2-3}-alkyl-

R^{18}, R^{19} independently of one another denotes H or C_{1-6}-alkyl,

R^{20} denotes halogen, hydroxy, cyano, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl- C_{1-3}-alkyl-, hydroxy-C_{1-3}-alkyl, R^{22}-C_{1-3}-alkyl or has one of the meanings given for R^{22},

R^{21} denotes C_{1-4}-alkyl, ω-hydroxy-C_{2-6}-alkyl, ω-C_{1-4}-alkoxy-C_{2-6}-alkyl, ω-C_{1-4}-alkyl-amino-C_{2-6}-alkyl, ω-di-(C_{1-4}-alkyl)-amino-C_{2-6}-alkyl, ω-cyclo-C_{3-6}-alkyleneimino-C_{2-6}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-4}-alkyl-carbonyl, carboxy, C_{1-4}-alkoxy-carbonyl, C_{1-4}-alkylsulphonyl, phenylcarbonyl or phenyl-C_{1-3}-alkyl-carbonyl,

R^{22} denotes phenyl, phenyl-C_{1-3}-alkoxy, C_{1-4}-alkoxy, C_{1-4}-alkylthio, carboxy, C_{1-4}-alkylcarbonyl, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, cyclo-C_{3-6}-alkyleneimino-carbonyl, C_{1-4}-alkyl-sulphonyl, C_{1-4}-alkyl-sulphinyl,

C_{1-4}-alkyl-sulphonylamino, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, cyclo-C_{3-6}-alkyleneimino, phenyl-C_{1-3}-alkylamino, N-(C_{1-4}-alkyl)-phenyl-C_{1-3}-alkylamino, acetylamino, propionylamino, phenylcarbonyl, phenylcarbonylamino, phenylcarbonylmethyl-amino, hydroxyalkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyr-rolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or alkylaminocarbonylamino,

while in the abovementioned groups and residues, particularly in A, B, W, X, Y, Z, R^1 to R^4, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^8, R^{10} to R^{22}, in each case one or more C atoms may additionally be mono- or polysubstituted with F and/or in each case one or two C atoms may additionally be monosubstituted independently of one another with Cl or Br and/or in each case one or more phenyl rings may additionally be substituted independently of one another may each have one, two or three substituents selected from among F, Cl, Br, I, C_{1-4}-alkyl, C_{1-4}-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, acetylamino, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, cyano, difluoromethoxy, trifluoromethoxy, amino-C_{1-3}-alkyl, C_{1-4}-alkylamino-C_{1-3}-alkyl- and di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkyl- and/or may be monosubstituted by nitro, and

the H atom of any carboxy group present or an H bonded to an N atom atom may be replaced in each case by a group which can be cleaved in vivo,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

with the proviso that if Y denotes phenylene substituted by -CN,
X denotes the bridge -CH_2-CH(OH)-CH_2-O-, Z is a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms and R^2 and R^3 denote H, W does not represent -$CR^{6a}R^{6b}$-O-.

The invention also relates to the compounds in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers and in the form of the free bases or the corresponding acid addition salts with pharmacologically safe acids. The subject of the invention also includes the compounds according to the invention, including their salts, wherein one or more hydrogen atoms are replaced by deuterium.

This invention also includes the physiologically acceptable salts of the amide compounds according to the invention as described above and hereinafter.

Also covered by this invention are pharmaceutical compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more inert carriers and/or diluents.

The present invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

The present invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, as an MCH antagonist, particularly as an MCH-1R antagonist.

The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of metabolic disorders and/or eating disorders, particularly obesity, including exogenic obesity, hyperinsulinary obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, central obesity and also bulimia, anorexia and hyperphagia.

The present invention further relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, reproductive disorders, memory disorders, forms of dementia and hormonal disorders.

The invention also relates to the use of at least one amide compound according to the invention and/ or a salt according to the invention, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, for preparing a pharmaceutical composition

which is suitable for the prevention and/or treatment of diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, cardiovascular diseases, particularly arteriosclerosis and high blood pressure and gonitis.

Furthermore the invention relates to processes for preparing a pharmaceutical composition according to the invention, characterised in that at least one amide compound according to the invention and/ or a salt according to the invention is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

The invention also relates to a pharmaceutical composition, containing a first active substance which is selected from the amide compounds according to the invention and/or the corresponding salts, including an amide compound of formula I wherein Y denotes phenylene substituted by -CN, X denotes the bridge $-CH_2-CH(OH)-CH_2-O-$, Z denotes a single bond, R^1 denotes a straight-chain or branched alkyl group with 1 to 10 C atoms, R^2 and R^3 denote H, W denotes $-CR^{6a}R^{6b}-O-$ and A, R^{6a}, R^{6b} have the meanings specified, and the salts thereof, as well as a second active substance which is selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression, optionally together with one or more inert carriers and/or diluents.

More detailed description of the invention

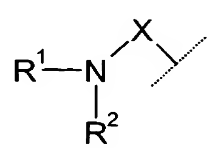
Unless otherwise specified the groups, residues and substituents, particularly A, B, W, X, Y, Z, R^1 to R^4, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^8, R^{10} to R^{22}, have the meanings given hereinbefore.

Preferably, the group R^3 denotes H or C_{1-4}-alkyl, more preferably H or methyl, particularly H.

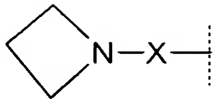
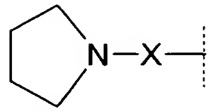
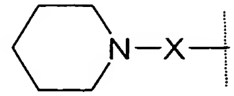
Preferably the groups R^1, R^2 independently of one another represent H, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, ω-hydroxy-C_{2-3}-alkyl, ω-(C_{1-4}-alkoxy)-C_{2-3}-alkyl, C_{1-4}-alkoxy-carbonyl-C_{1-4}-alkyl, carboxyl-C_{1-4}-alkyl, amino-C_{2-4}-alkyl, C_{1-4}-alkyl-amino-C_{2-4}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{2-4}-alkyl, cyclo-C_{3-6}-alkyleneimino-C_{2-4}-alkyl, pyrrolidinyl, pyrrolidinyl-C_{1-3}-alkyl, piperidinyl, piperidinyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, pyridyl or pyridyl-C_{1-3}-alkyl, while in the abovementioned groups and residues one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br, and the phenyl group may be mono- or polysubstituted by the above-defined group R^{12} and/or may be monosubstituted by nitro.

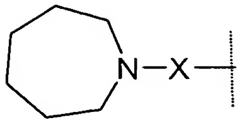
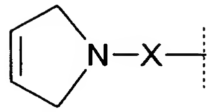
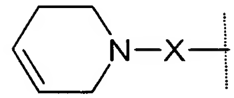
Particularly preferably at least one of the groups R^1, R^2 and most preferably both groups have a meaning other than H.

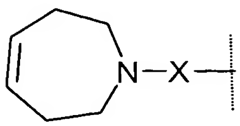
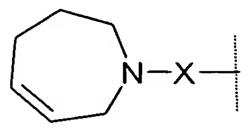
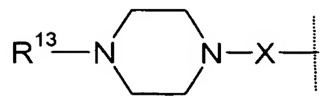
Also preferably, R^1 and R^2 form an alkylene bridge such that R^1R^2N- denotes a group selected from azetidine, pyrrolidine, piperidine, azepan, 2,5-dihydro-1H-pyrrole, 1,2,3,6-tetrahydro-pyridine, 2,3,4,7-tetrahydro-1H-azepine, 2,3,6,7-tetrahydro-1H-azepine, piperazine, wherein the free imine function is substituted by R^{13}, or morpholine and thiomorpholine, while according to the general definition of R^1 and R^2 one or more H atoms may be replaced by R^{14}, and/ or the abovementioned groups may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in a manner specified according to the general definition of R^1 and R^2 .

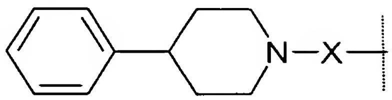
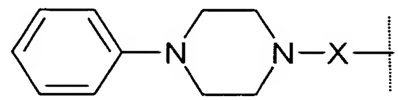
Particularly preferably the group 

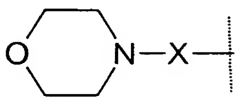
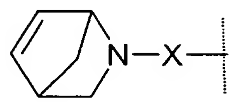
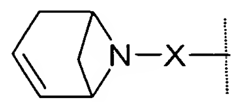
is defined according to one of the following partial formulae

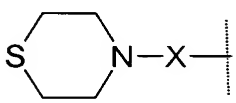
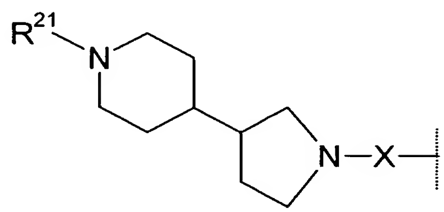
 ,  ,  ,

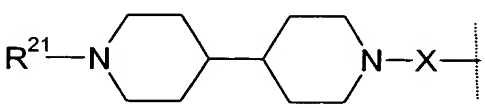
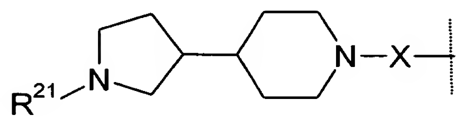
 ,  ,  ,

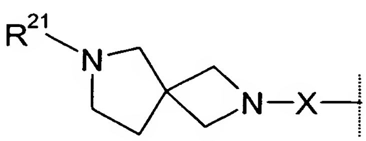
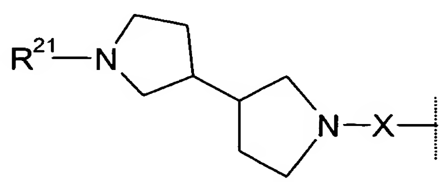
 ,  , 

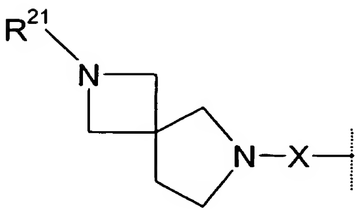
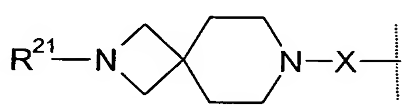
 ,  ,

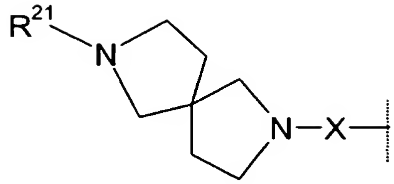
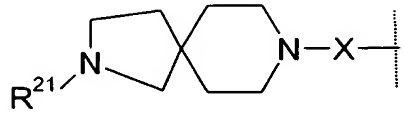
 ,  ,  ,

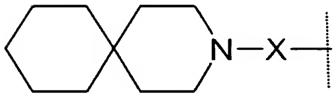
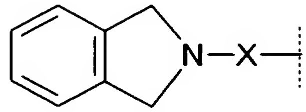
 , 

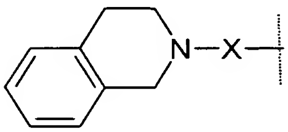
 , 

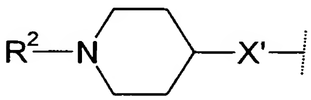
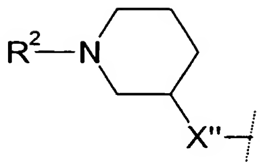
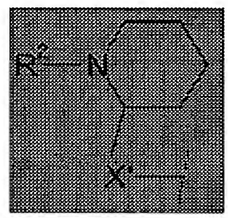
 , 

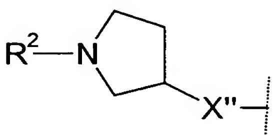
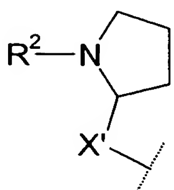
 ,  ,

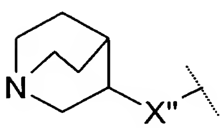
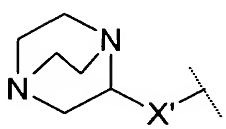
 ,  ,

 ,  ,

 ,

 ,  ,  ,

 ,  ,

 , 

wherein one or more H atoms of the heterocycle formed by the group R^1R^2N- may be replaced by R^{14} and the ring attached to the heterocycle formed by the group R^1R^2N- may be mono- or polysubstituted by R^{20} at one or more C atoms, or in the case of a phenyl ring may also additionally be monosubstituted by nitro and

X', X" independently of one another denote a single bond or C_{1-3}-alkylene and

in the event that the group Y is linked with X' or X" via a C atom, also denote -C_{1-3}-alkylene-O-, -C_{1-3}-alkylene-NH- or

-C_{1-3}-alkylene-N(C_{1-3}-alkyl)-, and

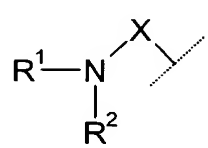
X" additionally also denotes -O-C_{1-3}-alkylene, -NH-C_{1-3}-alkylene or -N(C_{1-3}-alkyl)-C_{1-3}-alkylene and

in the event that the group Y is linked to X" via a C atom, also denotes -NH-, -N(C_{1-3}-alkyl)- or -O-,

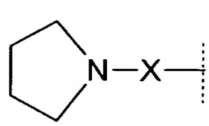
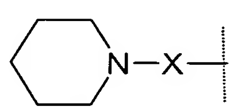
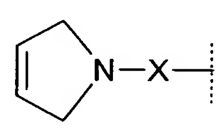
while in meanings given for X', X" hereinbefore in each case a C atom may be substituted by R^{10}, preferably by a hydroxy, ω-hydroxy-C_{1-3}-alkyl, ω-(C_{1-4}-alkoxy)-C_{1-3}-alkyl and/or C_{1-4}-alkoxy group, and/or one or two C atoms independently of one another in may each be substituted by one or two identical or different C_{1-4}-alkyl groups, and

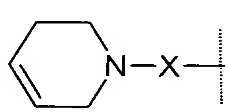
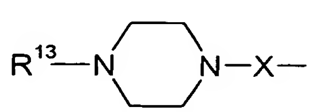
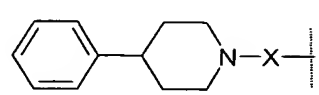
in X', X" independently of one another in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted by Cl or Br and

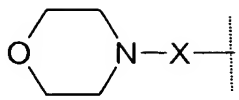
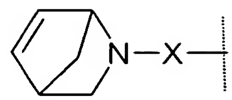
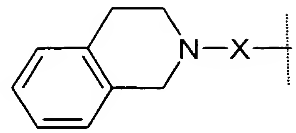
wherein R^2, R^{10}, R^{13}, R^{14}, R^{20}, R^{21} and X are defined as specified above and hereinafter.

Most particularly preferably, the group 

is defined according to one of the following partial formulae

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

wherein one or more H atoms of the heterocycle formed by the group R^1R^2N- may be replaced by R^{14} and the ring attached to the heterocycle formed by the group R^1R^2N- may be mono- or polysubstituted by R^{20} at one or more C atoms, and in the case of a phenyl ring may also additionally be monosubstituted by nitro.

If in the group X a $-CH_2-$ group of the alkylene bridge is replaced according to the invention, this $-CH_2-$ group is preferably not directly attached to a heteroatom, a double or triple bond.

Preferably the alkylene bridge X, X' or X" has no or at most one imino group. The position of the imino group within the alkylene bridge X, X' or X" is preferably selected so that no aminal function is formed together with the amino group NR^1R^2 or another adjacent amino group or two N atoms are not adjacent to each other.

Preferably X denotes an unbranched C_{1-4}-alkylene bridge and

in the event that the group Y is linked to X via a C atom, it also denotes $-CH_2-CH=CH-$, $-CH_2-C\equiv C-$, C_{2-4}-alkylenoxy or C_{2-4}-alkylene-NR^4,

while the bridge X may be attached to R^1 including the N atom attached to R^1 and X, forming a heterocyclic group, and

in X a C atom may be substituted by R^{10} and/or one or two C atoms in each case may be substituted by one or two identical or different C_{1-6}-alkyl groups and

in the abovementioned groups and residues one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br and

R^1, R^4 and R^{10} are as hereinbefore defined.

Particularly preferably X denotes $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-NR^4-CO-$ and

in the event that the group Y is linked to X via a C atom, it also denotes $-CH_2-CH=CH-$, $-CH_2-C\equiv C-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$ or $-CH_2-CH_2-NR^4-$ or $-CH_2-CH_2-CH_2-NR^4-$,

while the bridge X may be attached to R^1 including the N atom attached to R^1 and X, forming a heterocyclic group, and

while in X a C atom may be substituted by R^{10}, preferably a hydroxy, ω-hydroxy-C_{1-3}-alkyl, ω-(C_{1-4}-alkoxy)-C_{1-3}-alkyl and/or C_{1-4}-alkoxy group, and/or one or two C atoms independently of one another may each be substituted by one or two identical or different C_{1-4}-alkyl groups, and

in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted by Cl or Br.

#

Most particularly preferably, in the event that the group Y is linked to X via a C atom, X denotes $-CH_2-CH_2-O-$, which may be substituted as specified.

The group X preferably has no carbonyl group.

Advantageously, the group X defined as C_{2-4}-alkylenoxy, particularly $-CH_2-CH_2-CH_2-O-$, has no hydroxy substituents.

If Y denotes a condensed bicyclic ring system, the group X preferably denotes $-CH_2-$, $-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-$, particularly $-CH_2-CH_2-$, which may be substituted as specified.

If in the group X, X' or X" one or more C atoms is or are substituted by a hydroxy and/or C_{1-4}-alkoxy group, the substituted C atom is preferably not directly adjacent to another heteroatom.

Preferably Z denotes a single bond, $-CH_2-$ or $-CH_2-CH_2-$, while one or two C atoms independently of one another may be mono- or disubstituted by F, CH_3 or CF_3 and/or may be monosubstituted by Cl.

Particularly preferred meanings of the group Z are a single bond, $-CH_2$ or $-CH_2-CH_2$, particularly a single bond.

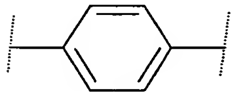
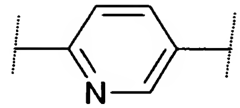
W preferably denotes $-CH_2-O-$, $-CH_2-NR^8-$, $-CH_2-CH_2-$ or -CH=CH-, wherein one or two C atoms may each be substituted independently of one another by F, CH_3 or CF_3. In the abovementioned definitions $-CH_2-O-$ and $-CH_2-NR^8-$ the group A is advantageously attached to the bridge W via a C atom.

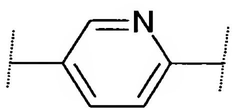
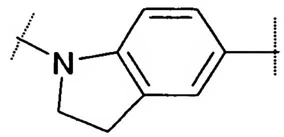
Particularly preferred definitions of the group W are $-CH_2-O-$, $-CH_2-NH-$, $-CH_2-NCH_3-$ and $-CH_2-CH_2-$, particularly $-CH_2-O-$.

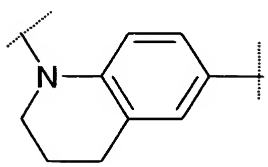
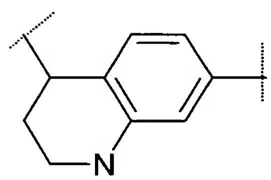
If the group W has the meaning given hereinbefore of an optionally substituted -CH=CH- bridge, the group Z is preferably a single bond.

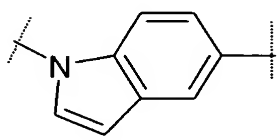
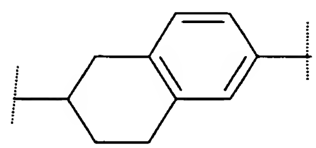
The group Y preferably has a meaning which is selected from the group of the bivalent cyclic groups phenyl, pyridinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl or tetrahydro-isoquinolinyl, while the abovementioned cyclic groups may be mono- or polysubstituted at one or more C atoms by R^{20}, or in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or substituted by R^{21}at one or more N atoms. R^1 may be attached to Y and/or X may be attached to Y as hereinbefore defined.

Particularly preferably, a definition of #the group Y is selected from among the bivalent cyclic groups

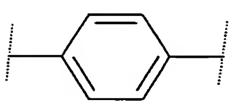
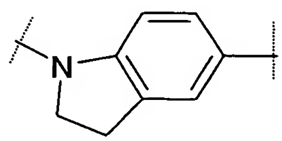
 ,  ,

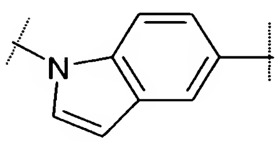
 ,  ,

 ,  ,

 ,  ,

and in particular Y has one of the following meanings

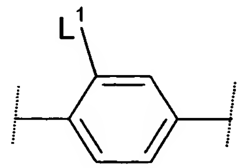
 ,  and

 .

The abovementioned cyclic groups may be mono- or polysubstituted at one or more C atoms by R^{20}, in the case of a phenyl group it may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21}.

If Y is a phenyl or pyridinyl group, the phenyl or pyridinyl group is at least monosubstituted, particularly in the event that the group W optionally denotes substituted -CH=CH- or $-CH_2-CH_2-$.

Most particularly preferably, the group Y denotes substituted phenylene of the partial formula



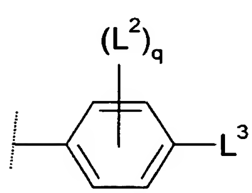
, wherein L^1 has one of the meanings given hereinbefore for R^{20} ,

preferably F, Cl, Br, I, CH_3, CF_3, OCH_3, OCF_3, CN or NO_2, or denotes H.

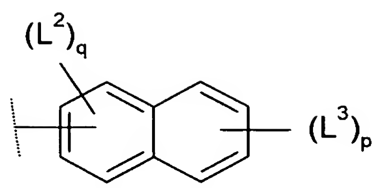
Preferably the group A is selected from among the bivalent cyclic groups phenyl, pyridinyl or naphthyl, which may be mono- or polysubstituted at one or more C atoms by R^{20}, and in the case of a phenyl ring may also additionally be monosubstituted by nitro.

Preferably the group A is mono-, di- or trisubstituted.

Particularly preferably the group A denotes substituted phenyl of the partial formula



or optionally substituted naphthyl of the partial formula



wherein

L^2 has one of the meanings given for R^{20} or denotes H, preferably F, Cl, Br, I, CH_3, CF_3, OCH_3, OCF_3, CN or NO_2,

L^3 has one of the meanings given for R^{20} or denotes H, preferably F, Cl, Br, I, CF_3, OCF_3, CN, NO_2, phenyl, C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-3}-alkyl, C_{1-4}-alkoxy, C_{3-7}-cycloalkyl-O, C_{3-7}-cycloalkyl-C_{1-3}-alkoxy, -COO-C_{1-4}-alkyl, -COOH, while the phenyl group may be mono- or polysubstituted by L^4, where L^4 has one of the meanings given for L^2,

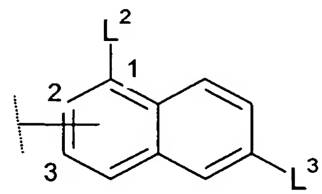
p, q is 0, 1 or 2,

with the proviso that the phenyl and naphthyl group may at most be only monosubstituted by nitro.

Particularly preferably, A is substituted phenyl according to the above partial formula, wherein q denotes 1 or 2 and/or at least one substituent L^2 is in the meta position to the substituent L^3.

In addition, A is, particularly preferably, substituted naphthyl according to the above partial formula, wherein q denotes 1 and/or p denotes 1.

A particularly preferred partial formula for A is



wherein the bond to the group W is made via the C atom at position number 2 or 3.

R^4 has one of the meanings given for R^{17}, preferably for R^{16}.

The groups R^{6a}, R^{6b} represent H, C_{1-4}-alkyl or CF_3, preferably H or methyl, particularly H.

The groups R^{7a}, R^{7b}, R^{7c}, R^{7d} represent H, F, C_{1-4}-alkyl or CF_3, preferably H or methyl, particularly H.

The group R^8 preferably denotes H or methyl.

If R^{11} is a C_{2-6}-alkenyl or C_{2-6}-alkynyl group, the definitions $-CH=CH_2$ and $-C\equiv CH$ are preferred.

The substituent R^{20} preferably does not contain any of the following structural elements:

a) -CO-aryl or -CO-heteroaryl, particularly -CO-phenyl, wherein heteroaryl, aryl and phenyl may be substituted,
b) -C(=NH)-NH-, wherein the H atoms may be substituted and/or
c) -NH-CO-NH-, wherein the H atoms may be substituted.

Preferred definitions of the group R^{20} are halogen, hydroxy, cyano, C_{1-4}-alkyl, C_{3-7}-cycloalkyl and C_{1-4}-alkoxy. Particularly preferably R^{20} denotes F, Cl, Br, I, OH, cyano, methyl, difluoromethyl, trifluoromethyl, ethyl, n-propyl, iso-propyl, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy or iso-propoxy.

Cy preferably denotes a C_{3-7}-cycloalkyl, particularly a C_{5-7}-cycloalkyl group, a C_{5-7}-cycloalkenyl group, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, aryl or heteroaryl, while aryl or heteroaryl preferably denotes a monocyclic or condensed bicyclic ring system, and the abovementioned cyclic groups may be mono- or polysubstituted at one or more C atoms by R^{20}, or in the case of a phenyl group also additionally monosubstituted by nitro, and/or one or more NH groups may be substituted by R^{21}.

Preferred compounds according to the invention are those wherein one or more of the groups, residues, substituents and/or indices have one of the meanings mentioned above as being preferred.

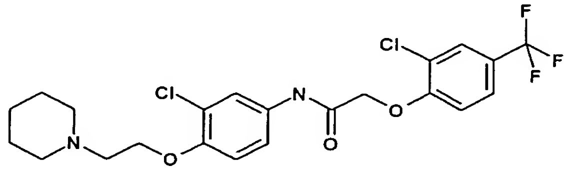
Particularly preferred compounds according to the invention are those wherein

Y denotes phenylene, 1H-indolylene or 2,3-dihydro-1H-indolylene according to the above definition described as being preferred, particularly phenylene substituted by L^1 according to the above partial formula and/or

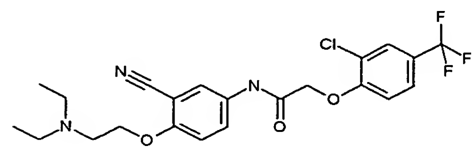
A denotes phenyl substituted by L^2 and L^3 according to the above partial formula.

Most particularly preferred according to the invention are those compounds wherein A, X, Y, Z, R^1, R^2, R^3 and W independently of one another have one or more of the preferred definitions specified above.

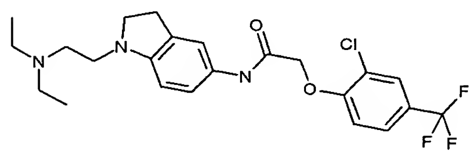
Particularly preferred are the following individual compounds:

(1) 

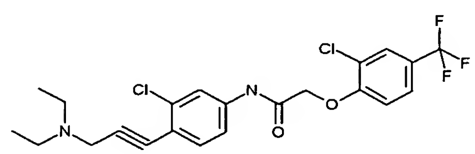
N-[3-chloro-4-(2-piperidin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(2) 

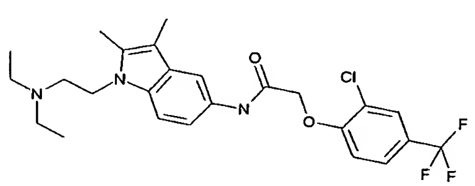
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[3-cyano-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(3) 

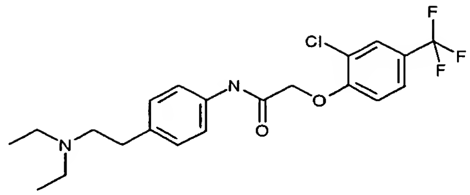
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[1-(2-diethylamino-ethyl)-2,3-dihydro-1*H*-indol-5-yl]-acetamide

(4) 

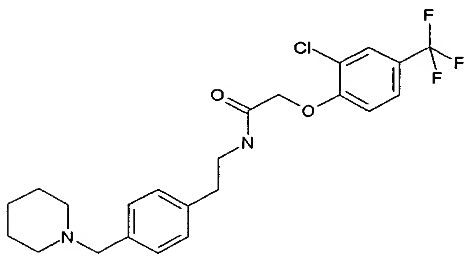
N-[3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(5) 

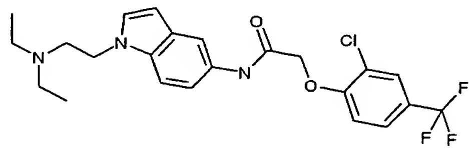
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[1-(2-diethylamino-ethyl)-2,3-dimethyl-1H-indol-5-yl]-acetamide

(6) 

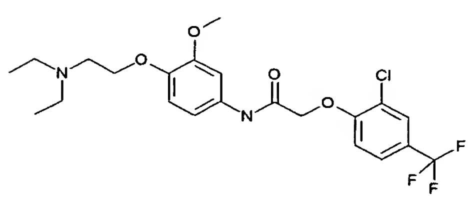
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[4-(2-diethylamino-ethyl)-phenyl]-acetamide

(7) 

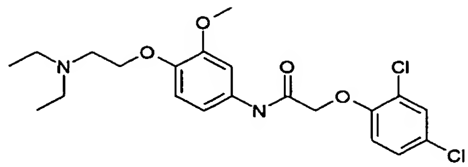
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-acetamide

(8) 

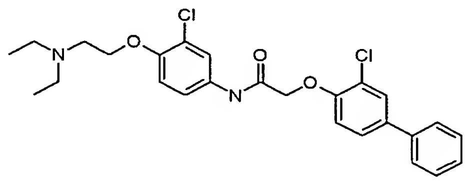
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[1-(2-diethylamino-ethyl)-1*H*-indol-5-yl]-acetamide

(9) 

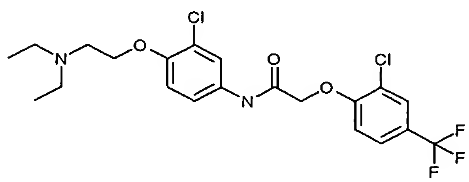
2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[4-(2-diethylamino-ethoxy)-3-methoxy-phenyl]-acetamide

(10) 

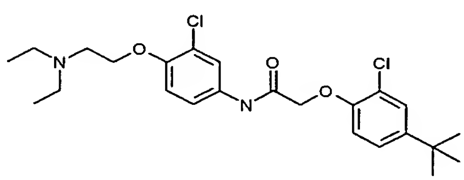
2-(2,4-dichloro-phenoxy)-*N*-[4-(2-diethylamino-ethoxy)-3-methoxy-phenyl]-acetamide

(11) 

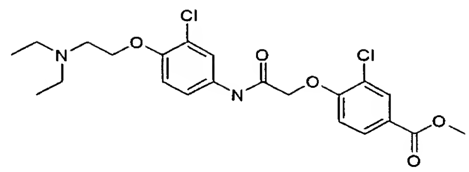
2-(3-chloro-biphenyl-4-yloxy)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(12) 

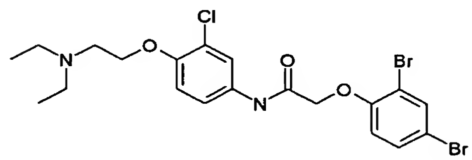
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(13) 

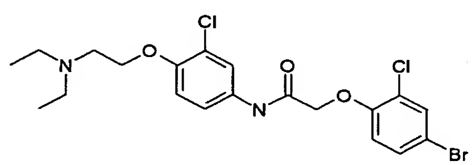
2-(4-*tert*-butyl-2-chloro-phenoxy)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(14) 

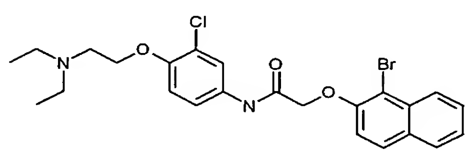
methyl 3-chloro-4-{[3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy}-benzoate

(15) 

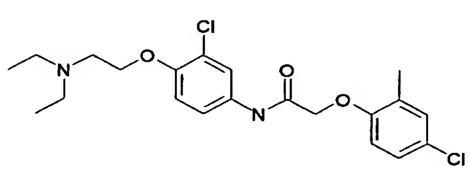
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2,4-dibromo-phenoxy)-acetamide

(16) 

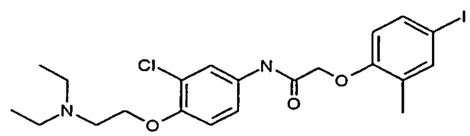
2-(4-bromo-2-chloro-phenoxy)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(17) 

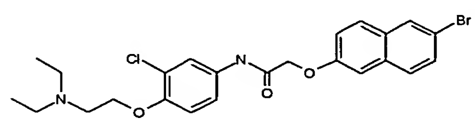
2-(1-bromo-naphthalen-2-yloxy)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(18) 

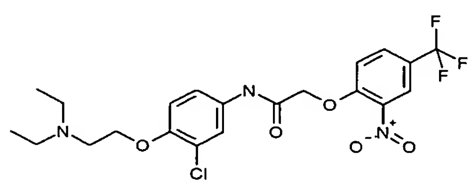
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(4-chloro-2-methyl-phenoxy)-acetamide

(19) 

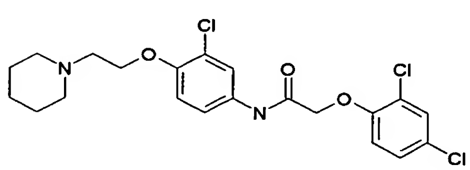
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(4-iodo-2-methyl-phenoxy)-acetamide

(20) 

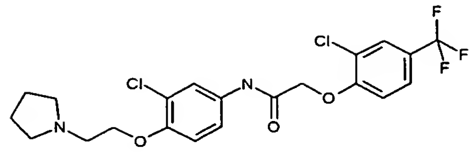
2-(6-bromo-naphthalen-2-yloxy)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

(21) 

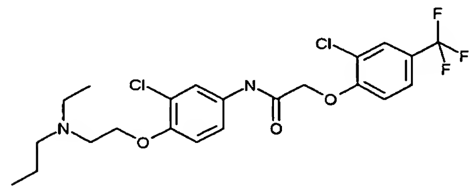
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-nitro-4-trifluoromethyl-phenoxy)-acetamide

(22) 

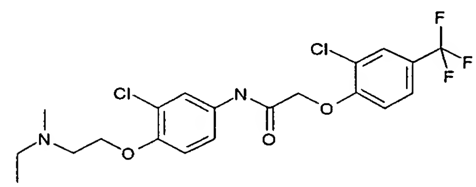
N-[3-chloro-4-(2-piperidin-1-yl-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide

(23) 

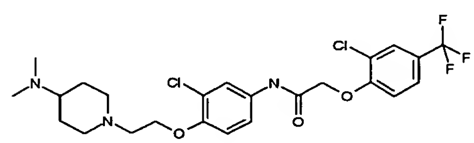
N-[3-chloro-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(24) 

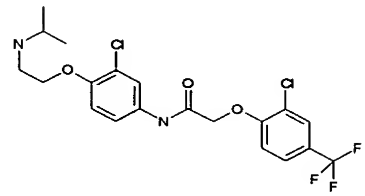
N-{3-chloro-4-[2-(ethyl-propyl-amino)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(25) 

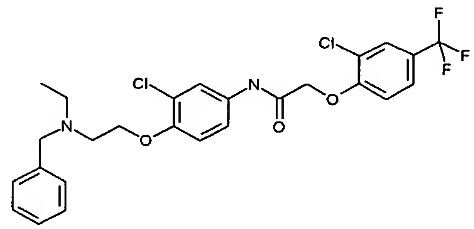
N-{3-chloro-4-[2-(ethyl-methyl-amino)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(26) 

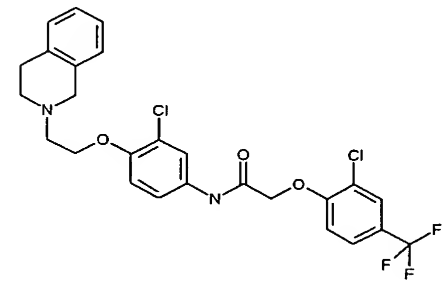
N-{3-chloro-4-[2-(4-dimethylamino-piperidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(27) 

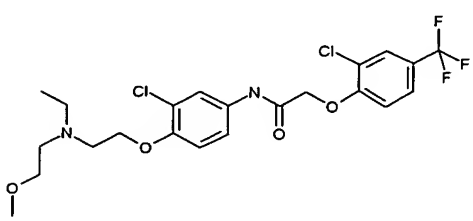
N-[3-chloro-4-(2-isopropylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(29) 

N-{4-[2-(benzyl-ethyl-amino)-ethoxy]-3-chloro-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

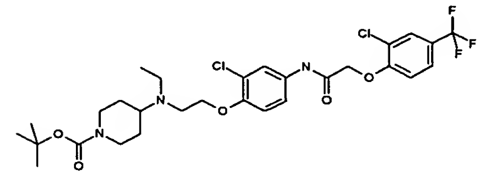
(30) 

N-{3-chloro-4-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

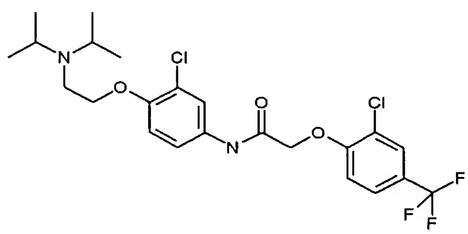
(31) 

N-(3-chloro-4-{2-[ethyl-(2-methoxy-ethyl)-amino]-ethoxy}-phenyl)-2-(2-

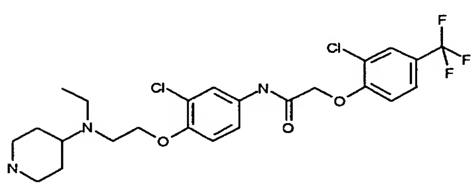
chloro-4-trifluoromethyl-phenoxy)-acetamide

(32) 

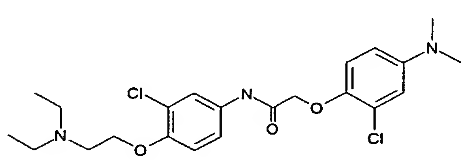
tert.butyl 4-[(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-ethyl-amino]-piperidin-1-carboxylate

(33) 

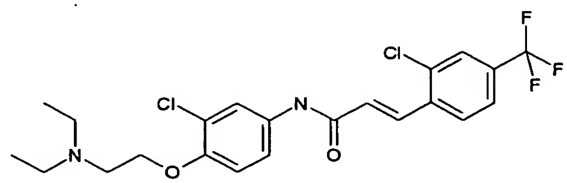
N-[3-chloro-4-(2-diisopropylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(34) 

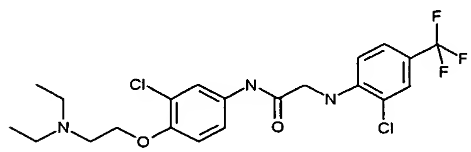
N-{3-chloro-4-[2-(ethyl-piperidin-4-yl-amino)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

(35) 

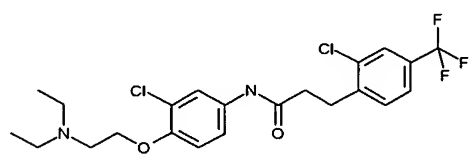
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-dimethylamino-phenoxy)-acetamide

(36) 

(E)-*N*-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

(37) 

N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenylamino)-acetamide

(38) 

N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-propionamide,

including the salts thereof.

Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

The term halogen denotes an atom selected from among F, Cl, Br and I, particularly F, Cl and Br.

The term C_{1-n}-alkyl, where n has a value of 3 to 8, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of

such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc.

The term C_{1-n}-alkylene, where n may have a value of 1 to 8, denotes a saturated, branched or unbranched hydrocarbon bridge with 1 to n C atoms. Examples of such groups include methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), 1-methyl-ethylene ($-CH(CH_3)-CH_2-$), 1,1-dimethyl-ethylene ($-C(CH_3)_2-CH_2-$), n-prop-1,3-ylene ($-CH_2-CH_2-CH_2-$), 1-methylprop-1,3-ylene ($-CH(CH_3)-CH_2-CH_2-$), 2-methylprop-1,3-ylene ($-CH_2-CH(CH_3)-CH_2-$), etc., as well as the corresponding mirror-symmetrical forms.

The term C_{2-n}-alkenyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C=C-double bond. Examples of such groups include vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc.

The term C_{2-n}-alkynyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C≡C-double bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, iso-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-methyl-1-propynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 3-methyl-2-butynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc.

The term C_{1-n}-alkoxy denotes a C_{1-n}-alkyl-O- group, wherein C_{1-n}-alkyl is defined as above. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n-hexoxy, iso-hexoxy etc.

The term C_{1-n}-alkylthio denotes a C_{1-n}-alkyl-S- group, wherein C_{1-n}-alkyl is defined as above. Examples of such groups include methylthio, ethylthio, n-

propylthio, iso-propylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, n-pentylthio, iso-pentylthio, neo-pentylthio, tert-pentylthio, n-hexylthio, iso-hexylthio, etc.

The term C_{1-n}-alkylcarbonyl denotes a C_{1-n}-alkyl-C(=O)- group, wherein C_{1-n}-alkyl is defined as above. Examples of such groups include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, iso-propylcarbonyl, n-butylcarbonyl, iso-butylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-hexylcarbonyl, etc.

The term C_{3-n}-cycloalkyl denotes a saturated mono-, bi-, tri- or spirocarbocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, bicyclo[3.2.1.]octyl, spiro[4.5]decyl, norpinyl, norbonyl, norcaryl, adamantyl, etc.

The term C_{5-n}-cycloalkenyl denotes a monounsaturated mono-, bi-, tri- or spirocarbocyclic group with 5 to n C atoms. Examples of such groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, etc.

The term C_{3-n}-cycloalkylcarbonyl denotes a C_{3-n}-cycloalkyl-C(=O) group, wherein C_{3-n}-cycloalkyl is defined as above.

The term aryl denotes a carbocyclic, aromatic ring system, such as for example phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl, etc.

The term heteroaryl used in this application denotes a heterocyclic, aromatic ring system which comprises in addition to at least one C atom one or more heteroatoms selected from N, O and/or S. Examples of such groups are furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,3,5-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-

oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinozilinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, etc. The term heteroaryl also comprises the partially hydrogenated heterocyclic, aromatic ring systems, particularly those listed above. Examples of such partially hydrogenated heterocycles are 2,3-dihydrobenzofuranyl, pyrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl, etc.

Terms such as aryl-C_{1-n}-alkyl, heteroaryl-C_{1-n}-alkyl, etc. refer to C_{1-n}-alkyl, as defined above, which is substituted with an aryl or heteroaryl group.

Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

The term "unsaturated", e.g. in "unsaturated carbocyclic group" or "unsaturated heterocyclic group", as used particularly in the definition of the group Cy, comprises, in addition to the mono- or polyunsaturated groups, the corresponding totally unsaturated groups, but particularly the mono- and diunsaturated groups.

The term "optionally substituted" used in this application indicates that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

The H atom of any carboxy group present or an H atom (imino or amino group) bonded to an N atom may in each case be replaced by a group which can be cleaved in vivo. By a group which can be cleaved in vivo from an N atom is meant for example a hydroxy group, an acyl group such as the

benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, *tert*.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl- C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO-O-(R_fCR_g)-O group wherein R_e to R_g are as hereinbefore defined,

while additionally the phthalimido group is a possibility for an amino group, and the abovementioned ester groups may also be used as groups which can be converted into a carboxy group in vivo.

The residues and substituents described above may be mono- or polysubstituted by fluorine as described. Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated alkylsulphinyl and alkylsulphonyl groups are trifluoromethylsulphinyl and trifluoromethylsulphonyl.

The compounds of general formula I according to the invention may have acid groups, predominantly carboxyl groups, and/or basic groups such as e.g.

amino functions. Compounds of general formula I may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

The compounds according to the invention may be obtained using methods of synthesis which are known in principle. Preferably the compounds are obtained analogously to the methods of preparation described more fully in the Examples that follow.

Stereoisomeric compounds of formula (I) may be separated in principle by conventional methods. The diastereomers may be separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

As already mentioned, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, in the case of acidically bound hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ion. The acid addition salts may be prepared, for example, using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of the above mentioned acids may be used. To prepare the alkali

and alkaline earth metal salts of the compound of formula (I) with acidically bound hydrogen the alkali and alkaline earth metal hydroxides and hydrides are preferably used, while the hydroxides and hydrides of the alkali metals, particularly sodium and potassium are preferred and sodium and potassium hydroxide are most preferred.

The compounds according to the present invention, including the physiologically acceptable salts, are effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit good affinity in MCH receptor binding studies. Pharmacological test systems for MCH-antagonistic properties are described in the following experimental section.

As antagonists of the MCH receptor the compounds according to the invention are advantageously suitable as pharmaceutical active substances for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have an intracerebral transitivity, particularly brain accessibility.

Therefore, MCH antagonists which contain at least one compound according to the invention, are particularly suitable in mammals, such as for example rats, mice, guinea pigs, hares, dogs, cats, sheep, horses, pigs, cattle, monkeys and also humans, for the treatment and/or prevention of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

Diseases caused by MCH or otherwise causally connected with MCH are particularly metabolic disorders, such as for example obesity, and eating disorders, such as for example bulimia, anorexia and hyperphagia. The indication obesity includes in particular exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile

obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity.

In addition, the diseases caused by MCH or otherwise causally connected with MCH also include hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affectivity disorders, depression, anxiety states, reproductive disorders, memory disorders, forms of dementia and hormonal disorders.

Compounds according to the invention are also suitable as active substances for the prevention and/or treatment of illnesses and/or disorders which accompany obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc., insulin resistance, pathological glucose tolerance, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, and gonitis.

MCH antagonists and formulations according to the invention may advantageously be used in combination with a dietary therapy, such as for example a dietary diabetes treatment, and exercise.

The dosage required to achieve such an effect is conveniently, by intravenous or subcutaneous route, 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of body weight, and by oral or nasal route or by inhalation, 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight, in each case 1 to 3 x daily.

For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances as described hereinafter, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty

substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments or suppositories.

For the above mentioned combinations it is possible to use as additional active substances particularly those which for example potentiate the therapeutic effect of an MCH antagonist according to the invention in terms of one of the indications mentioned above and/or which make it possible to reduce the dosage of an MCH antagonist according to the invention. Preferably one or more additional active substances are selected from among

- active substances for the treatment of diabetes,
- active substances for the treatment of diabetic complications,
- active substances for the treatment of obesity, preferably other than MCH antagonists,
- active substances for the treatment of high blood pressure,
- active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis,
- active substances for the treatment of anxiety states,
- active substances for the treatment of depression.

The above mentioned categories of active substances will now be explained in more detail by means of examples.

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins, α-glucosidase inhibitors, β3 adreno-receptor agonists.

Insulin sensitisers include pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702, GW-1929.

Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, trazamide, acetohexamide, glydlopyramide and its ammonium salts, glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

Biguanides include metformin, buformin and phenformin.

Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from Escherichi coli or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulation may also be obtained from insulin fragments or derivatives (for example INS-1, etc.).

Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two phase type", "intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

α-Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

β_3 Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease

inhibitors, glipazide, glyburide.

Active substances for the treatment of diabetic complications include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors.

Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

An example of a glycation inhibitor is pimagedine.

Protein Kinase C inhibitors are for example NGF, LY-333531.

Active substances other than those mentioned above for the treatment of diabetic complications include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

Active substances for the treatment of obesity, preferably other than MCH antagonists, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

Examples of preferred anorectics are phentermine, mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Active substances other than those mentioned above for the treatment of obesity include lipstatin.

Moreover for the purposes of this application the active substance group of anti-obesity active substances also includes the anorectics, of which the β_3 agonists, thyromimetic active substances and NPY antagonists

should be emphasised. The scope of the anti-obesity/anorectic active substances which are preferred here is indicated by the following additional list, by way of example: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dexfenfluramine or fenfluramine), a dopamine antagonist (such as for example bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist, an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat). Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the Glucagon-like Peptide-1 receptor, such as for example exendin and ciliary neurotrophic factors, such as for example axokine.

Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbeartan, CS-866, E4177.

Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 and their salts.

Fibrate compounds include bezafibrate, clinofibrate, clofibrate and simfibrate.

Active substances for the treatment of arthritis include ibuprofen.

Active substances for the treatment of anxiety states include chlordiazepoxide, diazepam, oxozolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

Active substances for the treatment of depression include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The dosage for these active substances is conveniently 1/5 of the lowest normal recommended dose up to 1/1 of the normal recommended dose.

The Examples that follow are intended to illustrate the invention:

Preliminary remarks:

As a rule, melting points, IR, UV, ^{1}H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated the R_f values were determined using ready-made silica gel 60 TLC plates F_{254} (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation. The ratios given for the eluants relate to units by volume of the solvent in question. For

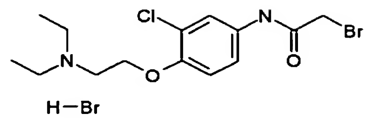
chromatographic purification, silica gel made by Messrs Millipore (MATREX^{TM}, 35-70my) was used.The HPLC data specified were measured under the parameters indicated below: Zorbax column (Agilent Technologies), SB (Stable Bond) - C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 µL; detection at 254 nm.
If there is no specific infomation as to the configuration, it is not clear whether there are pure enantiomers or whether partial or even total racemisation has taken place.

The following abbreviations are used above and hereinafter:

abs.	absolute
Boc	*tert*-butoxycarbonyl
CDI	N,N'-carbonyldiimidazole
CDT	N,N'-carbonyldi(1,2,4-triazole
DMF	N,N-dimethylformamide
ether	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
sat.	saturated
semiconc.	semiconcentrated
HCl	hydrochloric acid
HOAc	acetic acid
HOBt	1-hydroxybenzotriazole-hydrate
i. vac.	in vacuo (in vacuo)
KOH	potassium hydroxide
conc.	concentrated
MeOH	methanol
MTBE	methyl-*tert*-butylether
NaCl	sodium chloride
NaOH	sodium hydroxide
org.	organic
RT	ambient temperature
TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
TEBAC	triethylbenzylammonium chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
→*	denotes the binding site of a group

Synthesis of intermediate products

Intermediate product 1:



Z1a) [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine-hydrobromide

40.00 g (1.00 mol) of potassium carbonate was added to a solution of 50.00 g (0.288 mol) of 2-chloro-4-nitro-phenol and 60.23 g (0.350 mol) of (2-chloro-ethyl)-diethyl-amine in 700 mL DMF and the mixture was stirred for16 hours at 80°C. The reaction mixture was evaporated down i. vac., the residue was combined with water and the aqueous phase was exhaustively extracted with EtOAc. The combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac. The crude product was recrystallised from EtOAc and the mother liquor evaporated down i. vac. Purification of the residue by column chromatography (silica gel, gradient dichloromethane / MeOH 10:0 $\rightarrow$ 9:1) yielded the desired product.

Yield: 29.00 g (37 % of theory)

$C_{12}H_{17}ClN_2O_3$ (M= 272.734)

Calc.: Molpeak $(M+H)^+$: 273/275

Found: Molpeak $(M+H)^+$: 273/275 (Cl)

Z1b) 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine

A solution of 100 mL of conc. aqueous HCl in 100 mL EtOH was added dropwise to a suspension of 20.00 g (358 mmol) of iron powder and 20 g (73.33 mmol) of [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine in 200 mL EtOH, while the temperature was kept below 20 °C by cooling with ice. The reaction mixture was stirred for 30 minutes, neutralised with 10% aqueous sodium bicarbonate solution and was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The product was stored under a nitrogen atmosphere.

Yield: 17.40 g (98 % of theory)

$C_{12}H_{19}ClN_2O$ (M= 242.751)

Calc.: Molpeak$(M+H)^+$: 243/245

Found: Molpeak $(M+H)^+$: 243/245 (Cl)

R_f value: 0.6 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Z1c) 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide

A solution of 1.86 mL (21.00 mmol) of bromoacetylbromide in 10 mL of dichloromethane was added dropwise to a solution of 5.00 g (21.00 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine in 100 mL of dichloromethane at 0 °C and the mixture was stirred for 20 minutes at 0 °C. The precipitate formed was filtered off, washed with dichloromethane and MTBE and dried i. vac. at 40 °C.

Yield: 8.20 g (89 % of theory)

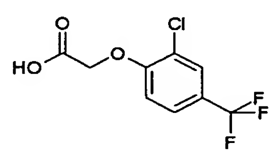
$C_{14}H_{21}BrClN_2O_2$ * Br (M= 444.597)

Calc.: Molpeak$(M+H)^+$: 363/365/367

Found: Molpeak $(M+H)^+$: 363/365/367 (BrCl)

HPLC-MS: 4.25 Min. (Stable Bond C18; 3.5 □m; water:acetonitrile:formic acid 9:1:0.01 → 1:9:0.01 over 9 min)

Intermediate product 2:



Z2a) ethyl (2-chloro-4-trifluoromethyl-phenoxy)-acetate

28.19 g (0.204 mol) of potassium carbonate was added to a solution of 20.00 g (0.102 mol) of 2-chloro-4-trifluoromethyl-phenol and 11.36 mL (0.102 mol) of ethyl bromo-acetate in 300 mL of DMF and the mixture was stirred for 7 hours at 60 °C and for 16 hours at RT. The reaction mixture was evaporated down i. vac. and the residue combined with EtOAc. The org. phase was washed with water, dried over magnesium sulphate and evaporated down i. vac.

Yield: 23.79 g (83% of theory)

$C_{11}H_{10}ClF_3O_3$ (M= 282.649)

Calc.: Molpeak$(M+Na)^+$: 305/307

Found: Molpeak $(M+Na)^+$: 305/307 (Cl)

R_f value: 0.58 (silica gel, petroleum ether / EtOAc 4:1)

Z2b) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid

84 mL of 2 M aqueous NaOH was added to a solution of 23.97 g (0.084 mol) of ethyl (2-chloro-4-trifluoromethyl-phenoxy)-acetate in 200 mL EtOH and the mixture was refluxed for 1 hour. EtOH was concentrated by evaporation i. vac., the residue was diluted with ice water and acidified with 2 M aqueous HCl. The precipitate formed was filtered off, washed with water and dried at 70 °C i. vac.

Yield: 12.33 g (58 % of theory)

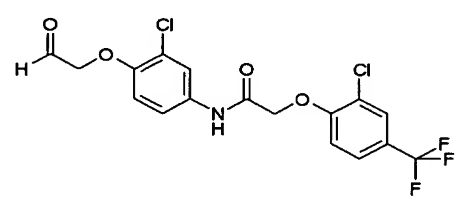
$C_9H_6ClF_3O_3$ (M= 254.595)

Calc.: Molpeak$(M-H)^-$: 253/255

Found: Molpeak $(M-H)^-$: 253/255 (Cl)

R_f value: 0.04 (silica gel, petroleum ether /EtOAc 3:2)

Intermediate product 3:



Z3a) 2-chloro-1-(2,2-diethoxy-ethoxy)-4-nitrobenzene

26.56 g (0.150 mol) of 2-chloro-4-nitrophenol and 24.25 mL (0.150 mol) of 2-bromo-1,1-diethoxy-ethane was added to a suspension of 22.80 g (0.165 mol) of potassium carbonate in 250 mL DMF and the mixture was heated to 140 °C for 24 hours. The reaction mixture was diluted with 1 L water and exhaustively extracted with MTBE. The combined org. extracts were washed with water,

dried over magnesium sulphate and evaporated down i. vac. Yield: 32.10 g (74 % of theory)

$C_{12}H_{16}ClNO_5$ (M= 289.718)

R_f value: 0.7 (silica gel, dichloromethane / cyclohexane / EtOAc 1:4:1)

Z3b) 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine

30 g (0.104 mol) of 2-chloro-1-(2,2-diethoxy-ethoxy)-4-nitrobenzene was added to a suspension of 1.50 g Pd/C (10 %) in 500 mL EtOAc and the mixture was hydrogenated for 2 hours at 20 psi. The catalyst was filtered off and the filtrate evaporated down i. vac.

Yield: 27.00 g (quantitative yield)

$C_{12}H_{18}ClNO_3$ (M= 259.735)

Calc.: Molpeak$(M+H)^+$: 260/262

Found: Molpeak $(M+H)^+$: 260/262 (Cl)

R_f value: 0.75 (silica gel, dichloromethane / MeOH 9:1)

Z3c) N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

4.495 g (0.028 mol) of CDI was added to a solution of 6.365 g (0.025 mol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (intermediate product 2b) in 100 mL abs. THF and the mixture was stirred for 30 minutes at 50 °C. 6.494 g (0.025 mol) of 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine was added and the mixture was stirred for 16 hours at RT. The reaction mixture was poured into ice water and stirred for 1 hour. The precipitate formed was filtered off, washed with water and dried at 50 °C.

Yield: 11.40 g (92 % of theory)

$C_{21}H_{22}Cl_2F_3NO_5$ (M= 496.314)

Calc.: Molpeak$(M-H)^-$: 494/496/498

Found: Molpeak $(M-H)^-$: 494/496/498 (Cl_2)

R_f value: 0.73 (silica gel, petroleum ether /EtOAc 3:2)

Z3d) N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

40 mL water and 130 mL TFA was added to a solution of 11.40 g (0.023 mol) of N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide in 130 mL chloroform at 0 °C and the mixture was stirred for 3.5 hours at 0 °C and for 48 hours at RT. The reaction mixture was neutralised with sat. aqueous sodium carbonate solution and exhaustively extracted with dichloromethane. The combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac.

Yield: 8.40g (86 % of theory)

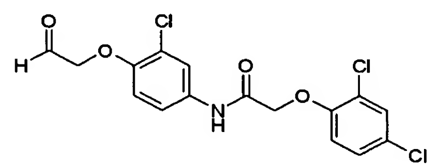
$C_{17}H_{12}Cl_2F_3NO_4$(M= 422.191)

Calc.: Molpeak$(M-H)^-$: 421/423/425

Found: Molpeak $(M-H)^-$: 421/423/425 (Cl_2)

R_f value: 0.14 (silica gel, petroleum ether /EtOAc 3:2)

Intermediate product 4:



Z4a) N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide

At 0 °C a solution of 0.57 g (2.38 mmol) of (2,4-dichloro-phenoxy)-acetylchloride in 4 mL dichloromethane was added dropwise to a solution of 0.50 g (2.16 mmol) of 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine (intermediate product Z3b) and 0.74 mL (4.32 mmol) of ethyl-diisopropylamine in 10 mL dichloromethane and the mixture was stirred for 1 hour at 0 °C. MeOH was added and the precipitated product was filtered off. The product was washed with MeOH and dried i. vac.

Yield: 0.74 g (79% of theory)

$C_{18}H_{18}Cl_3NO_5$ (M= 434.70)

Calc.: Molpeak$(M-H)^-$: 432/434/436

Found: Molpeak $(M-H)^-$: 432/434/436 (Cl_3)

HPLC-MS: 5.00 Min. (Devosil RPAqueous; 30-100% water / acetonitrile 70:30 $\rightarrow$ 0:100 in 5 Min.)

Z4b) N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide

At 0 °C 2 mL TFA and 0.15 mL water was added to a solution of 50 mg (0.011 mmol) of N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide in 2 mL dichloromethane and the mixture was stirred for 3.5 hours. 200 ml of 2 M aqueous sodium carbonate solution was added and exhaustively extracted with dichloromethane. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc / hexane 1:1).

Yield: 40 mg (89 % of theory)

$C_{16}H_{12}Cl_3NO_4$ (M= 388.63)

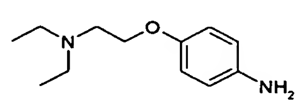
Calc.: Molpeak$(M-H)^-$: 386/388/390

Found: Molpeak $(M-H)^-$: 386/388/390 (Cl_3)

R_f value: 0.25 (silica gel, hexane / EtOAc 3:2)

HPLC-MS: 4.56 Min. (Devosil RPAqueous; 5-100% water / acetonitrile 70:30 → 0:100 in 5 Min.)

Intermediate product 5:



Z5a) Diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine

2.07 g (15.0 mmol) of potassium carbonate was added to a solution of 1.04 g (7.5 mmol) of 4-nitrophenol in 20 mL DMF under an argon atmosphere and the mixture was stirred for 20 minutes at 80 °C. 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride was added and the mixture was stirred for 8 hours at 90 °C. 100 ml of 2 M aqueous sodium carbonate solution was added and exhaustively extracted with ether. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The crude product was used in the next reaction step without further purification.

Yield: 1.59 g (89% of theory)

$C_{12}H_{18}N_2O_3$ (M= 238.28)

Calc.: Molpeak$(M+H)^+$: 239

Found: Molpeak $(M+H)^+$: 239

R_f value: 0.2 (silica gel, EtOAc)

Z5b) 4-(2-Diethylamino-ethoxy)-phenylamine

2.6 g (10.9 mmol) of diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine was added to a suspension of 130 mg Pd/C (10 %) in 20 mL MeOH and the mixture was hydrogenated for 4 hours. The catalyst was filtered off and the filtrate evaporated down i. vac.

Yield: 2.19 g (96% of theory)

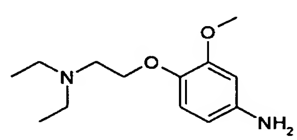
$C_{12}H_{20}N_2O$ (M= 208.30)

Calc.: Molpeak$(M+H)^+$: 209

Found: Molpeak $(M+H)^+$: 209

R_f value: 0.2 (silica gel, dichloromethane / MeOH 9:1)

Intermediate product 6:



Z6a) Diethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-amine

The product was obtained analogously to intermediate product Z5a starting from 1.27 g (7.5 mmol) of 2-methoxy-4-nitro-phenol and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 1.01 g (50 % of theory)

$C_{13}H_{20}N_2O_4$ (M= 268.31)

Calc.: Molpeak$(M+H)^+$: 269

Found: Molpeak $(M+H)^+$: 269

R_f value: 0.2 (silica gel, EtOAc)

Z6b) 4-(2-Diethylamino-ethoxy)-3-methoxy-phenylamine

0.77 g (2.87 mmol) of diethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-amine was added to a suspension of 1.00 g (17.9 mmol) of iron powder in 7 mL EtOH and the mixture was stirred for 10 minutes at RT. 6.6 mL of conc. aqueous HCl was added dropwise within 15 minutes and the mixture was stirred for 1 hour. 100 ml of 2 M sodium carbonate solution was added and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.62 g (92 % of theory)

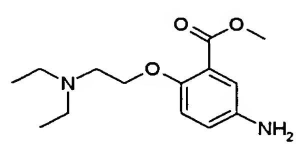
$C_{13}H_{22}N_2O_2$ (M= 238.33)

Calc.: Molpeak$(M+H)^+$: 269

Found: Molpeak $(M+H)^+$: 269

R_f value: 0.05 (silica gel, dichloromethane / MeOH 9:1)

Intermediate product 7:



Z7a) methyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate

The product was obtained analogously to intermediate product Z5a starting from 1.48 g (7.5 mmol) of methyl 2-hydroxy-5-nitro-benzoate and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 0.81 g (40 % of theory)

$C_{14}H_{20}N_2O_5$ (M= 296.32)

Calc.: Molpeak$(M+H)^+$: 297

Found: Molpeak $(M+H)^+$: 297

R_f value: 0.1 (silica gel, EtOAc / MeOH 9:1)

Z7b) methyl 5-amino-2-(2-diethylamino-ethoxy)-benzoate

The product was obtained analogously to intermediate product Z5b starting from 400 mg (1.35 mmol) of methyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate.

Yield: 0.35 g (97 % of theory)

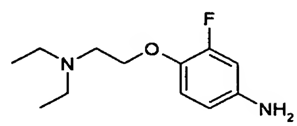
$C_{14}H_{22}N_2O_3$ (M= 266.34)

Calc.: Molpeak$(M+H)^+$: 267

Found: Molpeak $(M+H)^+$: 267

R_f value: 0.2 (silica gel, EtOAc / MeOH 9:1)

Intermediate product 8:



Z8a) diethyl-[2-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine

The product was obtained analogously to intermediate product Z5a starting from 1.18 g (7.5 mmol) of 2-fluoro-4-nitro-phenol and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride erhalten.

Yield: 1.65 g (86 % of theory)

$C_{12}H_{17}FN_2O_3$ (M= 256.27)

Calc.: Molpeak$(M+H)^+$: 257

Found: Molpeak $(M+H)^+$: 257

R_f value: 0.1 (silica gel, EtOAc)

Z8b) 4-(2-diethylamino-ethoxy)-3-fluoro-phenylamine

The product was obtained analogously to intermediate product Z6b starting from 0.68 g (2.65 mmol) of diethyl-[2-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine.

Yield: 0.60 g (quantitative yield)

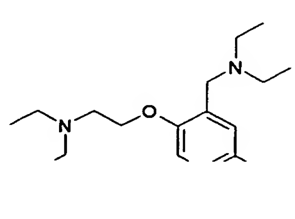
$C_{12}H_{19}FN_2O$ (M= 226.29)

Calc.: Molpeak$(M+H)^-$: 227

Found: Molpeak $(M+H)^+$: 227

R_f value: 0.1 (silica gel, dichloromethane / MeOH 9:1)

Intermediate product 9:



Z9a) tert.butyl (3-diethylaminomethyl-4-hydroxy-phenyl)-carbaminate

At 80 °C a solution of 0.90 g (4.11 mmol) of Boc-anhydride in 20 mL THF was added to a solution of 1.00 g (3-74 mmol) of 4-amino-2-diethylaminomethyl-phenol and 0.52 mL (3.74 mmol) of triethylamine in 20 mL abs. THF and the mixture was refluxed for 24 hours. 100 ml of 2 M aqueous sodium carbonate solution was added and the mixture was exhaustively extracted with ether. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc).

Yield: 1.03 g (94 % of theory)

$C_{16}H_{26}N_2O_3$ (M= 294.39)

Calc.: Molpeak$(M+H)^-$: 295

Found: Molpeak $(M+H)^+$: 295

R_f value: 0.3 (silica gel, EtOAc)

Z9b) tert.butyl [4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenyl]-carbaminate

The product was obtained analogously to intermediate product Z5a starting from 2.21 g (7.5 mmol) of tert.butyl (3-diethylaminomethyl-4-hydroxy-phenyl)-carbaminate and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 0.88 g (30 % of theory)

$C_{22}H_{39}N_3O_3$ (M= 393.56)

Calc.: Molpeak$(M+H)^+$: 394

Found: Molpeak $(M+H)^+$: 394

R_f value: 0.05 (silica gel, dichloromethane / MeOH 9:1)

Z9c) 4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenylamine

5 mL TFA was added to a solution of 0.18 g (0.457 mmol) of tert.butyl [4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenyl]-carbaminate in 5 mL chloroform and the mixture was stirred for 1 hour at RT. 100 ml of 2 M aqueous sodium carbonate solution was added and exhaustively extracted

with ether. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.13 g (97 % of theory)

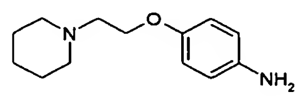
$C_{17}H_{31}N_3O$ (M= 293.45)

Calc.: Molpeak$(M+H)^+$: 294

Found: Molpeak $(M+H)^+$: 294

R_f value: 0.05 (silica gel, dichloromethane / MeOH 4:1)

Intermediate product 10:



Z10) 4-(2-piperidin-1-yl-ethoxy)-phenylamine

15.4 g (111.00 mmol) of potassium carbonate was added to a solution of 4.0 g (27.86 mmol) of 4-amino-2-chlorophenol and 5.1 g (27.86 mmol) of 1-(2-chloro-ethyl)-piperidine in 50 mL acetonitrile and the mixture was stirred for 48 hours at RT. The solvent was evaporated off i. vac., the residue was combined with water and the aqueous phase was exhaustively extracted with EtOAc. The combined org. extracts were washed with water, dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

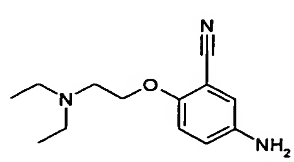
Yield: 77 mg (61 % of theory)

$C_{13}H_{19}ClN_2O$ (M= 254.762)

Calc.: Molpeak$(M+H)^+$: 255/257

Found: Molpeak $(M+H)^+$: 255/257 (Cl)

Intermediate product 11:



Z11a) 2-hydroxy-5-nitro-benzonitrile

At 45-50 °C a solution of 36.0 mL of 65% aqueous nitric acid in 50 mL conc. acetic acid was added dropwise to a solution of 50 g (0.416 mol) of 2-hydroxy-benzonitrile in 150 mL conc. acetic acid and the mixture was stirred for 1 hour at 50 °C. The reaction mixture was cooled to RT, diluted with 400 mL water and the precipitate formed was filtered off (mixture of o- and p-substituted product). The mother liquor was diluted with 1 L ice water and the precipitate formed was filtered off (product). The product mixture was dissolved in dichloromethane / MeOH and purified by column chromatography (silica gel, gradient dichloromethane / MeOH 10:0 → 4:1).

Yield: 25.22 g (37 % of theory)

$C_7H_4N_2O_3$ (M= 164.122)

Calc.: Molpeak$(M-H)^-$: 163

Found: Molpeak $(M-H)^-$: 163

R_f value: 0.35 (silica gel, dichloromethane / MeOH 9:1)

Z11b) 5-amino-2-hydroxy-benzonitrile

4.50 g (27.00 mmol) of 2-hydroxy-5-nitro-benzonitrile was added to a suspension of 0.45 g Pd/C (10 %) in 45 mL EtOAc and the mixture was hydrogenated for 1.5 hours under 3 bar H_2 atmosphere. The catalyst was filtered off and the residue dried i. vac.

Yield: 3.40 g (94 % of theory)

$C_7H_6N_2O$ (M= 134.139)

Calc.: Molpeak$(M-H)^-$: 133

Found: Molpeak $(M-H)^-$: 133

R_f value: 0.3 (silica gel, dichloromethane / MeOH 9:1)

Z11c) 5-amino-2-(2-diethylamino-ethoxy)-benzonitrile

11.06 g (0.080 mol) of potassium carbonate was added to a solution of 2.683 g (0.020 mol) of 5-amino-2-hydroxy-benzonitrile and 3.786 g (0.022 mol) of N,N-diethylamino-ethylchoride-hydrochloride in 100 mL abs. acetonitrile and the mixture was stirred for 48 hours at RT. The solvent was evaporated off i.

vac. and the residue was combined with water. The aqueous phase was exhaustively extracted with EtOAc, the combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Yield: 0.80 g (17 % of theory)

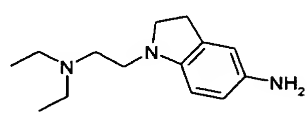
$C_{13}H_{19}N_3O$ (M= 233.316)

Calc.: Molpeak$(M+H)^+$: 234

Found: Molpeak $(M+H)^+$: 234

R_f value: 0.15 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Intermediate product 12:



Z12a) diethyl-[2-(5-nitro-2,3-dihydro-indol-1-yl)-ethyl]-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.477 g (2.905 mmol) of 5-nitro-2,3-dihydro-1H-indole and 0.500 g (2.905 mmol) of N,N-diethylamino-ethylchoride-hydrochloride in 5 mL DMF and the mixture was stirred for 16 hours at 90 °C. The reaction mixture was diluted with water and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, EtOAc).

Yield: 0.14 g (18 % of theory)

$C_{14}H_{21}N_3O_2$ (M= 263.342)

Calc.: Molpeak$(M+H)^+$: 264

Found: Molpeak $(M+H)^+$: 264

R_f value: 0.26 (silica gel, EtOAc / MeOH 9:1)

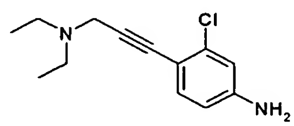
Z12b) 1-(2-diethylamino-ethyl)-2,3-dihydro-1H-indol-5-ylamine

140 mg (0.532 mmol) of diethyl-[2-(5-nitro-2,3-dihydro-indol-1-yl)-ethyl]-amine was added to a suspension of 50 mg of Raney-Ni in 5 mL MeOH and the

mixture was hydrogenated for 1 hour at RT under 20 psi of H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac. The crude product was reacted immediately without any further purification (cf. Example 12).

Yield: 80 mg (64 % of theory)

Intermediate product 13:



Z13a) [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine

Under a nitrogen atmosphere 12.5 mL (0.090 mol) of 3-N,N-diethylamino-propyne was added to 25.00 g (0.106 mol) of 4-bromo-3-chloro-nitrobenzene, 43.7 mL (0.315 mol) of triethylamine, 10.40 g (0.009 mol) of tetrakis[triphenylphosphine]-palladium(II) and 1.71 g (0.009 mol) of copper(I)-iodide in 250 mL acetonitrile and the mixture was refluxed for 18 hours. The reaction mixture was evaporated down i. vac., combined with EtOAc and the organic phase was washed with water. The org. phase was evaporated down i. vac. and the residue was purified by column chromatography (silica gel, petroleum ether / EtOAc 10:0 $\rightarrow$ 4:1) followed by column chromatography (silica gel, dichloromethane).

Yield: 15.0 g (62 % of theory)

$C_{13}H_{15}ClN_2O_2$ (M= 266.730)

Calc.: Molpeak$(M+H)^+$: 267/269

Found: Molpeak $(M+H)^+$: 267/269 (Cl)

Z13b) 3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenylamine

A solution of 15 mL of conc. aqueous HCl in 15 mL EtOH was added to a suspension of 4.189 g (75.00 mmol) of iron powder and 2.00 g (7.50 mmol) of [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine in 20 mL of EtOH with vigorous stirring and the mixture was stirred for 30 minutes. The reaction mixture was neutralised with 200 mL of 10 % aqueous sodium carbonate

solution and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

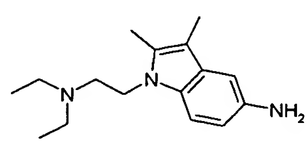
Yield: 0.45 g (25 % of theory)

$C_{13}H_{17}ClN_2$ (M= 236.747)

Calc.: Molpeak$(M+H)^+$: 237/239

Found: Molpeak $(M+H)^+$: 237/239 (Cl)

Intermediate product 14:



Z14a) [2-(2,3-dimethyl-5-nitro-indol-1-yl)-ethyl]-diethyl-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.553 g (2.905 mmol) of 2,3-dimethyl-5-nitro-1H-indole and 0.500 g (2.905 mmol) of N,N-diethylamino-ethylchoride-hydrochloride in 5 mL DMF and the mixture was stirred for 16 hours at 90 °C. The reaction mixture was diluted with water and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 0.15 g (18 % of theory)

$C_{16}H_{23}N_3O_2$ (M= 289.3812)

Calc.: Molpeak$(M+H)^+$: 290

Found: Molpeak $(M+H)^+$: 290

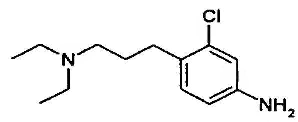
R_f value: 0.54 (silica gel, EtOAc / MeOH 9:1)

Z14b) 1-(2-diethylamino-ethyl)-2,3-dimethyl-1H-indol-5-ylamine

150 mg (0.518 mmol) of [2-(2,3-dimethyl-5-nitro-indol-1-yl)-ethyl]-diethyl-amine was added to a suspension of 100 mg of Raney-Ni in 5 mL MeOH and the mixture was hydrogenated for 1 hour at RT under 20 psi H_2 atmosphere.

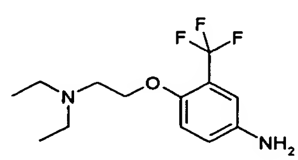
The catalyst was filtered off and the filtrate evaporated down i. vac. The crude product was reacted immediately without further purification (see Example 5).
Yield: 100 mg (74 % of theory)

Intermediate product 15:



Z15) 3-chloro-4-(3-diethylamino-propyl)-phenylamine
2.00 g (7.498 mmol) of 3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenylamine (intermediate product Z13b) was added to a suspension of 0.50 g Raney-Ni in 50 mL abs. MeOH and the mixture was hydrogenated for 2.5 hours at RT and 50 psi H_2 atmosphere. The catalyst was filtered off, the filtrate evaporated down i. vac. and the residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).
Yield: 0.90 g (50 % of theory)
$C_{13}H_{21}ClN$ (M= 240.779)
Calc.: Molpeak$(M+H)^+$: 241/243
Found: Molpeak $(M+H)^+$: 241/243 (Cl)

Intermediate product 16:



Z16a) diethyl-[2-(4-nitro-2-trifluoromethyl-phenoxy)-ethyl]-amine
5.60 g (40.00 mmol) of potassium carbonate was added to a solution of 4.10 g (20.00 mmol) of 4-nitro-2-trifluoromethyl-phenol (J. Org. Chem. 1962, 27, 4660-4662.) in 40 mL DMF and the mixture was heated to 80 °C. A solution of

3.5 g (20.00 mmol) of N,N-diethylamino-ethylchoride-hydrochloride in 10 mL DMF was added dropwise and the mixture was stirred for a further 3 hours at 80 °C. The reaction mixture was diluted with 100 mL sat. aqueous NaCl solution and exhaustively extracted with EtOAc. The combined org. extracts were washed with 10 % aqueous sodium carbonate solution, dried over magnesium sulphate and evaporated down i. vac.

Yield: 7.5 g (80 % of theory)

$C_{13}H_{17}F_3N_2O_3$ (M= 306.287)

Calc.: Molpeak$(M+H)^+$: 307

Found: Molpeak $(M+H)^+$: 307

Z16b) 4-(2-diethylamino-ethoxy)-3-trifluoromethyl-phenylamine

7.0 g (22.854 mmol) of 4-(2-diethylamino-ethoxy)-3-trifluoromethyl-phenylamine was added to a suspension of 0.50 g Pd/C (10 %) in EtOAc and the mixture was hydrogenated for 6 hours at 50 °C and 50 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac. MTBE was added and the org. phase was washed several times with water, dried over magnesium sulphate, filtered through activated charcoal and evaporated down i. vac.

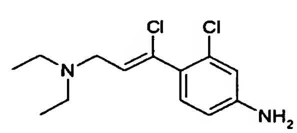
Yield: 4.40 g (70 % of theory)

$C_{13}H_{19}F_3N_2O$ (M= 276.304)

Calc.: Molpeak$(M+H)^+$: 277

Found: Molpeak $(M+H)^+$: 277

Intermediate product 17:



Z17) 3-chloro-4-((Z)-1-chloro-3-diethylamino-propenyl)-phenylamine

A solution of 15 mL conc. aqueous HCl in 15 mL EtOH was added to a suspension of 2.20 g (75.00 mmol) of iron powder and 2.20 g (8.25 mmol) of [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine (intermediate product Z13a) in 20 mL EtOH with vigorous stirring and the mixture was stirred for 2

hours at 80 °C. The reaction mixture was neutralised with 200 mL 10 % aqueous sodium carbonate solution and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac.

Yield: 1.70 g (75 % of theory)

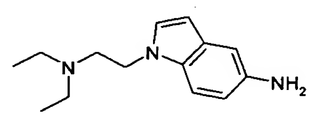
$C_{13}H_{18}Cl_2N_2$ (M= 273.208)

Calc.: Molpeak$(M+H)^+$: 273/275/277

Found: Molpeak $(M+H)^+$: 273/275/277 (Cl_2)

R_f value: 0.71 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1)

Intermediate product 18:



Z18a) diethyl-[2-(5-nitro-indol-1-yl)-ethyl]-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.47 g (2.905 mmol) of 5-nitro-1H-indole and 0.50 g (2.905 mmol) of N,N-diethylamino-ethylchoride-hydrochloride in 5 mL DMF and the mixture was stirred for 3 hours at 80 °C. The reaction mixture was diluted with water and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.65g (86 % of theory)

$C_{14}H_{19}N_3O_2$ (M= 261.326)

Calc.: Molpeak$(M+H)^+$: 262

Found: Molpeak $(M+H)^+$: 264

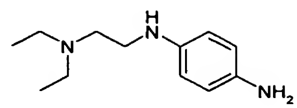
Z18b) 1-(2-diethylamino-ethyl)-1H-indol-5-ylamine

650 mg (2.487 mmol) of diethyl-[2-(5-nitro-indol-1-yl)-ethyl]-amine was added to a suspension of 200 mg Raney-Ni in 10 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

Yield: 520 mg (90 % of theory)

$C_{14}H_{21}N_3$ (M= 231.344)
Calc.: Molpeak$(M+H)^+$: 232
Found: Molpeak $(M+H)^+$: 232

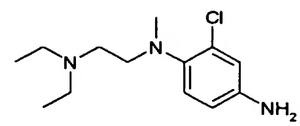
Intermediate product 19:



Z19a) N'-(2-chloro-4-nitro-phenyl)-N,N-diethyl-ethane-1,2-diamine
25 mL of 50 % aqueous KOH solution was added to a solution of 1.00 g (5.795 mmol) of 2-chloro-4-nitro-phenylamine, 2.995 g (17.384 mmol) of (2-chloro-ethyl)-diethyl-amine and 0.66 g (2.898 mmol) of TEBAC in 50 mL toluene and the mixture was refluxed for 5 days. The reaction mixture was cooled to RT and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH 4:1).
Yield: 1.2 g (76 % of theory)
$C_{12}H_{18}ClN_3O_2$ (M= 271.749)
Calc.: Molpeak$(M+H)^+$: 272/274
Found: Molpeak $(M+H)^+$: 272/274 (Cl)

Z19b) N-(2-diethylamino-ethyl)-benzene-1,4-diamine
1.20 mg (4.416 mmol) of N'-(2-chloro-4-nitro-phenyl)-N,N-diethyl-ethane-1,2-diamine was added to a suspension of 200 mg Raney-Ni in 20 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.
Yield: 800 mg (87 % of theory)
$C_{12}H_{21}N_3$ (M= 207.321)
Calc.: Molpeak$(M+H)^+$: 207
Found: Molpeak $(M+H)^+$: 207

Intermediate product 20:



Z20a) N-(2-chloro-4-nitro-phenyl)-N',N'-diethyl-N-methyl-ethane-1,2-diamine
1.00 mL (6.181 mmol) of N,N-diethyl-N'-methyl-ethane-1,2-diamine was added to a solution of 1.085 g (6.181 mmol) of 2-chloro-1-fluoro-4-nitrobenzene and 1.03 mL (7.417 mmol) of triethylamine in 20 mL THF and the mixture was stirred for 48 hours at RT. The reaction mixture was combined with sat. aqueous sodium bicarbonate solution and exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 1.60 mg (91 % of theory)

$C_{13}H_{20}ClN_3O_2$ (M= 285.776)

Calc.: Molpeak(M+H)$^+$: 286/288

Found: Molpeak (M+H)$^+$: 286/288 (Cl)

Z20b) 2-chloro-N^1-(2-diethylamino-ethyl)-N^1-methyl-benzene-1,4-diamine
1.60 mg (5.599 mmol) of N-(2-chloro-4-nitro-phenyl)-N',N'-diethyl-N-methyl-ethane-1,2-diamine was added to a suspension of 200 mg Raney-Ni in 20 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

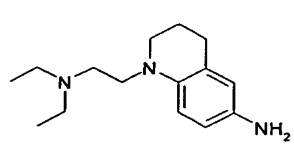
Yield: 1.30 mg (91 % of theory)

$C_{13}H_{22}ClN_3$ (M= 255.793)

Calc.: Molpeak(M+H)$^+$: 256/258

Found: Molpeak (M+H)$^+$: 256/258

Intermediate product 21:



Z21a) N-[1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-2,2,2-trifluoro-acetamide

50 mL of 50 % aqueous KOH solution was added to a solution of 3.00 g (12.284 mmol) of 6-nitro-1,2,3,4-tetrahydro-quinoline, 6.342 g (36.852 mmol) of (2-chloro-ethyl)-diethyl-amine and 1.68 g (7.370 mmol) of TEBAC in 100 mL toluene and the mixture was stirred for 1 hour at 80 °C. The reaction mixture was cooled to RT and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 0.75 g (18 % of theory)

$C_{17}H_{24}F_3N_3O$ (M= 343.396)

Calc.: Molpeak$(M+H)^+$: 344

Found: Molpeak $(M+H)^+$: 344

Z21b) 1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-ylamine

1.1 mL 6 M aqueous NaOH solution was added to a solution of 0.75 g (2.184 mmol) of N-[1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-2,2,2-trifluoro-acetamide in 5 mL MeOH at 0 °C and the mixture was stirred for 15 minutes at 0 °C and for 1 hour at RT. The reaction mixture was evaporated down i. vac., sat. aqueous sodium bicarbonate solution was added and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

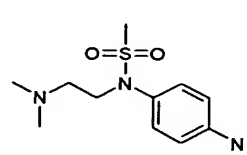
Yield: 220 mg (41 % of theory)

$C_{15}H_{25}N_3$ (M= 247.387)

Calc.: Molpeak$(M+H)^+$: 248

Found: Molpeak $(M+H)^+$: 248

Intermediate product 22:



Z22a) N-(4-nitro-phenyl)-methanesulphonic acid amide

27.60 g (0.20 mol) of 4-nitroaniline was dissolved in 100 mL pyridine. At 0°C 16.3 mL (0.21 mol) of methanesulphonic acid chloride were added dropwise so that the reaction temperature did not exceed 20-25°C. Then the mixture was stirred for 2.5 hours at RT. The reaction mixture was added to 800 mL ice water with stirring and stirred for 30 minutes. The precipitated solid was filtered off, washed with 500 mL water and 100 mL EtOH and dried.

Yield: 41.00 g (95 % of theory)

melting point: 183-184°C

R_f value: 0.50 (silica gel, dichloromethane / EtOAc = 90:10)

Z22b) N-(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-methanesulphonic acid amide

36.00 g (0.166 mol) of N-(4-nitro-phenyl)-methanesulphonic acid amide was dissolved in 2000 mL acetone. The solution was combined with 47.8 g (0.332 mol) of 1-chloro-2-dimethylaminoethane * HCl, 68.8 g (0.498 mol) of potassium carbonate, 5.0 g (0.033 mol) of sodium iodide and 50 mL water. It was refluxed for 16 hours with stirring. After the addition of another 23.9 g (0.166 mol) of 1-chloro-2-dimethylaminoethane * HCl, 45.9 g (0.332 mol) of potassium carbonate and 5.0 g (0.033 mol) of sodiumiodide, the mixture was refluxed for 5 hours with stirring. At RT the inorganic salts were filtered off. The filtrate was evaporated down i. vac. and the residue dissolved in EtOAc. The org. phase was washed 2x with semisat. aqueous sodium chloride solution, dried over magnesium sulphate, filtered and evaporated down i. vac.

Yield: 30.57 g (64 % of theory)

$C_{11}H_{17}N_3O_4S$ (M= 287.340)

Calc.: Molpeak$(M+H)^+$: 288

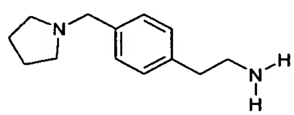
Found: Molpeak $(M+H)^+$: 288

R_f value: 0.60 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1)

Z22c) N-(4-amino-phenyl)-N-(2-dimethylamino-ethyl)-methanesulphonic acid amide

9.00 g (31.3 mmol) of N-(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-methanesulphonic acid amide were dissolved in 120 mL MeOH. After the addition of 1.0 g of 10% palladium/charcoal the mixture was hydrogenated for 1 hour at RT and 50 psi H_2 atmosphere. The reaction mixture was filtered and the filtrate evaporated down i. vac. The residue was stirred with ether/petroleum ether = 1:1. The solid was filtered off, washed with ether/petroleum ether = 1:1 and dried.
Yield: 7.65 g (95 % of theory)
melting point: 151-152°C
R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1)

Intermediate product 23:



Z23a) ethyl 4-cyanomethyl-benzoate
A solution of 500 g (2.057 mol) of ethyl 4-bromomethyl-benzoate in 1000 ml of ethanol is added dropwise to a solution of 147.5 g (2.263 mol) of potassium cyanide in 250 ml of hot water. The reaction mixture is refluxed for one hour and stirred for 12 hours at RT. A further 73.7 g (0.5 mol) of potassium cyanide are added and the mixture is refluxed for two hours. The solid present in the reaction mixture is filtered off and the filtrate is filtered through a mixture of silica gel and activated charcoal. The filtrate obtained is evaporated down and the residue is poured onto 1000 ml of water. The aqueous solution is extracted with MTBE and the organic phase is extracted three times with water. Then the organic phase is dried over magnesium sulphate and the solvent is distilled off using the rotary evaporator. The product is purified by column chromatography on silica gel (petroleum ether/ ethyl acetate 8:2).
Yield: 164.46 g (42.2 % of theory)
$C_{11}H_{11}NO_2$ (M= 189.216)

Calc.: Molpeak $(M+H)^+$: 190

Found: Molpeak $(M+H)^+$: 190

R_f value: 0.3 (silica gel, petroleum ether/EtOAc 8:2)

Z23b) 4-cyanomethyl-benzoic acid

A solution of 10 g (53 mol) of ethyl 4-cyanomethyl-benzoate and 2.02 ml of a 1 M sodium hydroxide solution in 100 ml of ethanol is refluxed for one hour. Then the reaction solution is evaporated down and the residue is combined with ice water. Concentrated hydrochloric acid is added dropwise to the reaction solution until no more precipitate is formed. The precipitate is filtered off, washed twice with water and dried.

Yield: 4.7 g (55 % of theory)

$C_9H_7NO_2$ (M= 161,162)

Calc.: Molpeak $(M-H)^-$: 160

Found: Molpeak $(M-H)^-$: 160

Z23c) (4-hydroxymethyl-phenyl)-acetonitrile

5.17 g (32 mol) of CDI are added to a solution of 4.7 g (29 mol) of 4-cyanomethyl-benzoic acid in 250 ml of tetrahydrofuran and stirred until no more gas is given off. This reaction mixture is added dropwise to a solution of 3.29 g (87 mol) of sodium borohydride in 200 ml of water in such a way that the temperature does not exceed 30°C. The mixture is stirred for two hours and the reaction mixture is adjusted to pH 3-4 with potassium hydrogen sulphate solution. Then it is extracted with EtOAc, the organic phase is dried over magnesium sulphate and the solvent is separated off using the rotary evaporator.

Yield: 2.6 g (60.9 % of theory)

C_9H_9NO (M= 147.178)

Calc.: Molpeak$(M-H)^-$: 146

Found: Molpeak $(M-H)^-$: 146

Z23d) (4-bromomethyl-phenyl)-acetonitrile

0.86 ml (9 mmol) of phosphorus tribromide are added dropwise to a solution of 2.6 g (17.66 mmol) of (4-hydroxymethyl-phenyl)-acetonitrile in 25 ml MTBE at 0°C. After the reaction has ended the reaction mixture is combined with water at RT, the organic phase is separated off and these are extracted successively with sodium hydrogen carbonate solution and water. The organic phase is dried over magnesium sulphate and the solvent is distilled off using the rotary evaporator.

Yield: 2.9 g (78.1 % of theory)

C_9H_8BrN (M= 210.075)

Calc.: Molpeak$(M+H)^+$: 209/211

Found: Molpeak $(M+H)^+$: 209/211

Z23e) (4-pyrrolidin-1-ylmethyl-phenyl)-acetonitrile

0.446 ml (5.44 mmol) of pyrrolidine and 1.366 g (9.882 mmol) of potassium carbonate are added to 20 ml of dimethylformamide. 1.038 g (4.941 mmol) of (4-bromomethyl-phenyl)-acetonitrile are added with stirring and the mixture is stirred for 12 hours at RT. The reaction mixture is evaporated down in the rotary evaporator and the residue is extracted with ethyl acetate and water. The organic phase is dried over magnesium sulphate and the solvent is removed using the rotary evaporator.

Yield: 0.732 g (74 % of theory)

$C_{13}H_{16}N_2$ (M= 200,286)

Calc.: Molpeak$(M+H)^+$: 201

Found: Molpeak $(M+H)^+$: 201

R_f value: 0.5 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Z23f) 2-(4-pyrrolidin-1-ylmethyl-phenyl)-ethylamine

A reaction mixture of 0.73 g (3.66 mmol) of (4-pyrrolidin-1-ylmethyl-phenyl)-acetonitrile and 0.1 g Raney nickel in 25 ml of methanolic ammonia solution is hydrogenated for 9 hours at 50°C under 3 bar hydrogen.

Yield: 0.72 g (96.4 % of theory)

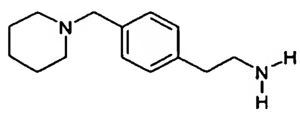
$C_{13}H_{20}N_2$ (M= 204.31)

Calc.: Molpeak$(M+H)^+$: 205

Found: Molpeak $(M+H)^+$: 205

R_f value: 0.23 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Intermediate product 24



Z24a) (4-piperidin-1-ylmethyl-phenyl)-acetonitrile

Prepared analogously to Example Z23e from piperidine and (4-bromomethyl-phenyl)-acetonitrile.

Yield: 1.6 g (39 % of theory)

$C_{14}H_{18}N_2$(M= 214.31)

Calc.: Molpeak$(M+H)^+$: 215

Found: Molpeak $(M+H)^+$: 215

R_f value: 0.4 (silica gel, cyclohexane/EtOAc 1:1)

Z24b) 2-(4-piperidin-1-ylmethyl-phenyl)-ethylamine

Prepared analogously to Example Z23f from (4-piperidin-1-ylmethyl-phenyl)-acetonitrile

Yield: 1.4 g (85.9 % of theory)

$C_{14}H_{22}N_2$ (M= 218.34)

Calc.: Molpeak$(M+H)^+$: 219

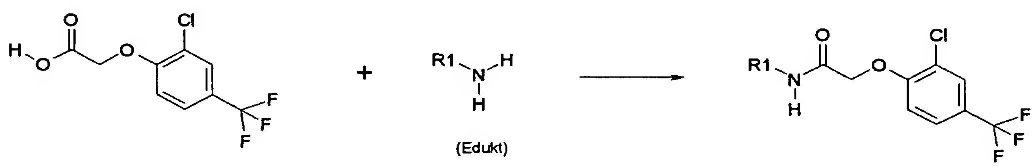
Found: Molpeak $(M+H)^+$: 219

R_f value: 0.2 (silica gel, dichloromethane/ethanol/ammonia 20:1:0.1)

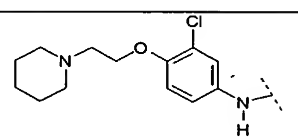
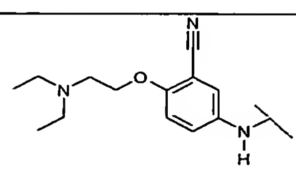
General working method I (TBTU coupling):

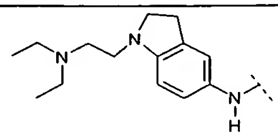
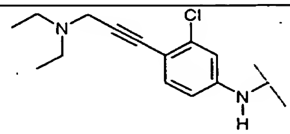
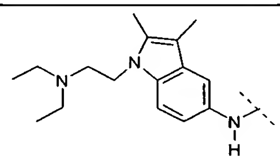
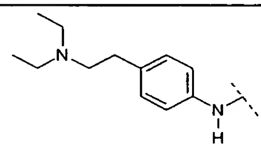
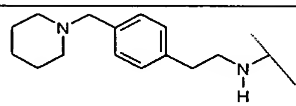
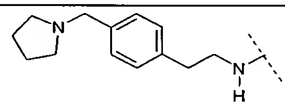
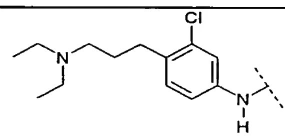
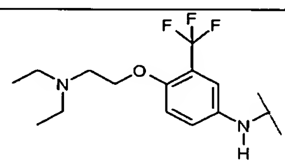
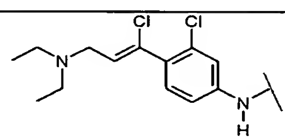
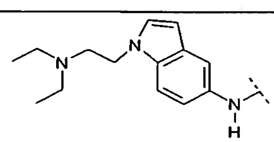
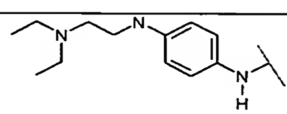
Triethylamine (1.5 eq.) or N-ethyldiisopropylamine (1.5eq.) and TBTU (1.0-1.5 eq.) are added successively to a solution of carboxylic acid (1.0 eq.) in THF or DMF. Depending on the carboxylic acid the mixture is stirred for 10 minutes - 12 hours between ambient temperature and 40°C before the amine (1.0 eq.) is added. The reaction is stirred for 30 minutes - 24 hours between ambient temperature and 40°C, before semisaturated $NaHCO_3$ solution is added. After extraction of the aqueous phase with EtOAc the organic phase is dried over magnesium sulphate. The solvent is removed using the rotary evaporator; further purification is carried out by column chromatography or crystallisation. The reaction may also be carried out in a Chemspeed automatic synthesiser.

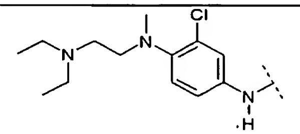
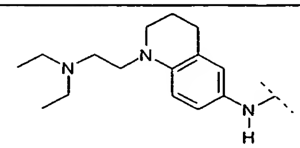
The following compounds were prepared according to general working method I:



while in the Table that follows the products are defined by the partial formula R^1-NH- and the associated carboxylic acid educts are defined by reference to the corresponding Example number of the intermediate product.

Example	R^1NH-	Educt	Empirical formula	Mass spectrum	R_f value	Yield (%)
1		Z10	$C_{22}H_{23}Cl_2F_3N_2O_3$	491/493 $[M+H]^+$	0.45 (A)	44
2		Z11b	$C_{22}H_{23}ClF_3N_3O_3$	470/472 $[M+H]^+$	0.36 (A)	64

3		Z12b	$C_{23}H_{27}ClF_3N_3O_2$	470/472 [M+H]$^+$	0.22 (A)	44
4		Z13b	$C_{22}H_{21}Cl_2F_3N_2O_2$	473/475/477 [M+H]$^+$	0.42 (A)	21
5		Z14b	$C_{25}H_{29}ClF_3N_3O_2$	496/498 [M+H]$^+$	0.30 (A)	48
6		Lit.	$C_{21}H_{24}ClF_3N_2O_2$	429/431 [M+H]$^+$	0.33 (A)	36
7		Z24b	$C_{23}H_{26}ClF_3N_2O_2$	455/457 [M+H]$^+$	0.46 (A)	50
8		Z23f	$C_{22}H_{24}ClF_3N_2O_2$	441/443 [M+H]$^+$	0.37 (A)	46
9		Z15	$C_{22}H_{25}Cl_2F_3N_2O_2$	477/479/481 [M+H]$^+$	0.22 (A)	31
10		Z16b	$C_{22}H_{23}ClF_6N_2O_3$	513/515 [M+H]$^+$	0.27 (A)	39
11		Z17	$C_{22}H_{22}Cl_3F_3N_2O_2$	509/11/13/15 [M+H]$^+$	0.48 (A)	1
12		Z18b	$C_{23}H_{25}ClF_3N_3O_2$	468/470 [M+H]$^+$	0.63 (A)	1
13		Z19b	$C_{21}H_{25}ClF_3N_3O_2$	444/446 [M+H]$^+$	0.35 (A)	35

14		Z20b	$C_{22}H_{26}Cl_2F_3N_3O_2$	492/494/496 $[M+H]^+$	0.46 (A)	49
15		Z21b	$C_{24}H_{29}ClF_3N_3O_2$	484/486 $[M+H]^+$	0.86 (B)	42

Lit.: known from the literature

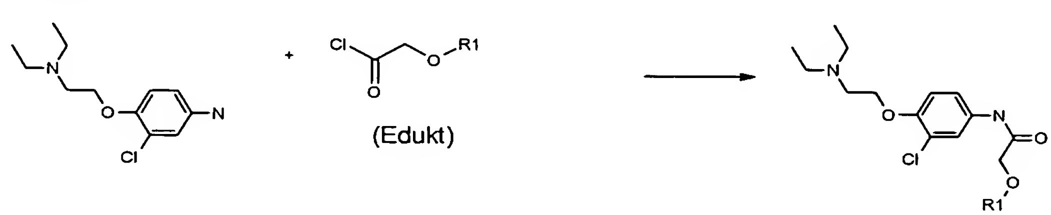
Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

B) EtOAc / MeOH / conc. aqueous ammonia = 90:10:1

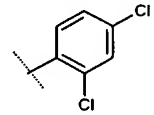
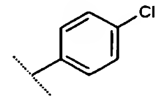
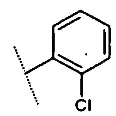
<u>General working method II:</u>

A solution of 1.0 eq. acid chloride in THF is slowly added dropwise to a solution of 1.0 eq. of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine and 4.5-6.0 eq. of triethylamine in THF at 5°C. The reaction mixture is stirred for 3 hours at 25-30°C, filtered off and washed with THF. The filtrate is evaporated down i. vac. and the residue purified by column chromatography. The intermediate product is dissolved in acetonitrile, acidified with ethereal HCl and precipitated with ether. Further purification is carried out by recrystallisation.

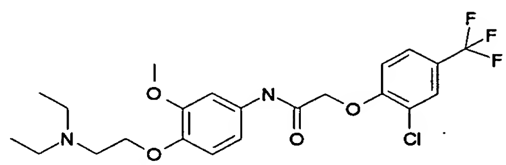
According to general working method II the following compounds were prepared:



while in the Table that follows the products are defined by means of the group R^1-. The associated amino educts are commercially available and/or known from the literature.

Example	R^1	Empirical formula	Melting point	Yield (%)
16		$C_{20}H_{23}Cl_3N_2O_3$ x HCl	186-188°C	63
17		$C_{20}H_{24}Cl_2N_2O_3$ x HCl	171-172°C	62
18		$C_{20}H_{24}Cl_2N_2O_3$ x HCl	183-185°C	63

Example 19:



19) 2-(2-chloro-4-trifluoromethyl-phenoxy)-*N*-[4-(2-diethylamino-ethoxy)-3-methoxy-phenyl]-acetamide

171 mg (0.82 mmol) of CDI was added to a solution of 185 mg (0.73 mmol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (cf intermediate product Z2b) in 5 mL tetrahydrofuran and the reaction mixture was stirred for 30 minutes at 50°C. Then 0.1 mL (0.73 mmol) of triethylamine and 200 mg (0.73 mmol) of 4-(2-diethylamino-ethoxy)-3-methoxy-phenylamine (see intermediate product Z6b) were added and the solution was stirred for 16 hours at RT. The reaction solution was added to water and stirred for 45 minutes at RT. After filtration the residue was dried in the circulating air dryer.

Yield: 170 mg (49 % of theory)

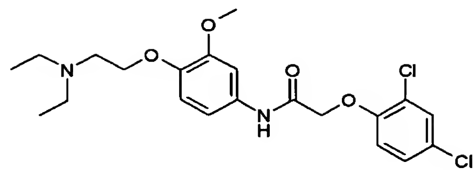
$C_{22}H_{26}ClF_3N_2O_4$ (M= 474.912)

Calc.: Molpeak$(M+H)^+$: 475/477

Found: Molpeak $(M+H)^+$: 475/477 (Cl)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 20:



20) 2-(2,4-dichloro-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-methoxy-phenyl]-acetamide

A solution of 70 mg (0.290 mmol) of (2,4-dichloro-phenoxy)-acetylchloride in 0.5 mL dichloromethane was added to a solution of 66 mg (0.278 mmol) of 4-(2-diethylamino-ethoxy)-3-methoxy-phenylamine (intermediate product Z6b) and 96 µL (0.56 mmol) of ethyl-diisopropylamine in 1.5 mL abs. dichloromethane and the mixture was stirred for 15 hours at RT. The reaction mixture was evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH 9:1).

Yield: 77 mg (61 % of theory)

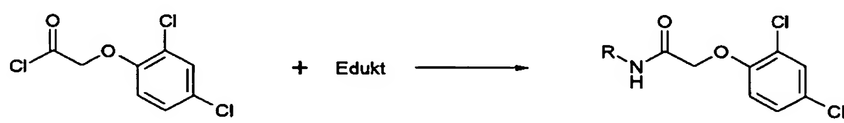
$C_{21}H_{26}Cl_2N_2O_4$ (M= 441.358)

Calc.: Molpeak$(M+H)^+$: 441/443/445

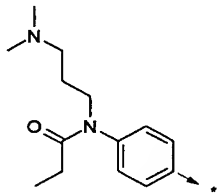
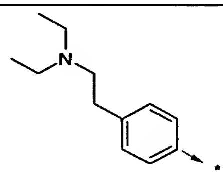
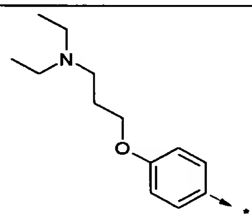
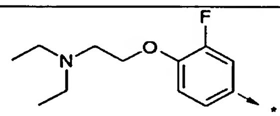
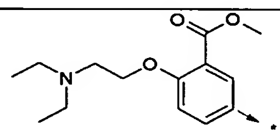
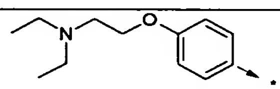
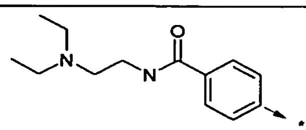
Found: Molpeak $(M+H)^+$: 441/443/445

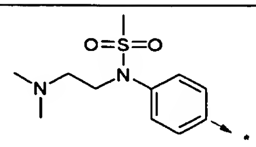
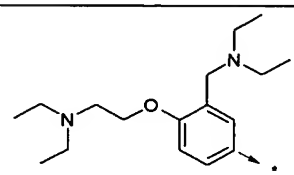
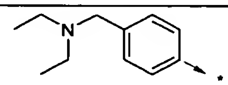
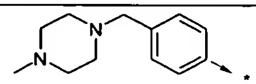
R_f value: 0.32 (silica gel, dichloromethane / MeOH 9:1)

The following compounds were prepared analogously to Example 20:



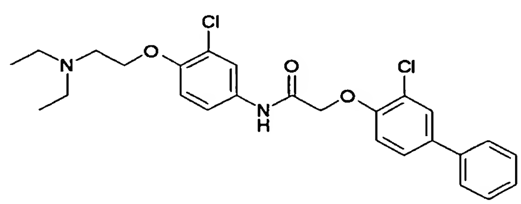
while in the Table that follows the products are defined by means of the group R and the associated educts are defined by reference to the corresponding Example number of the intermediate product or are given as known from the literature (Lit.).

Example	R	Educt	Empirical formula	Mass spectrum	R_f value	Yield (%)
21		Lit.	$C_{22}H_{27}Cl_2N_3O_3$	452/454/457 $[M+H]^+$	0.12 (A)	65 %
22		Lit.	$C_{20}H_{24}Cl_2N_2O_2$	395/397/399 $[M+H]^+$	0.38 (A)	46 %
23		Lit.	$C_{21}H_{26}Cl_2N_2O_3$	425/427/429 $[M+H]^+$	0.31 (A)	69 %
24		Z8b	$C_{20}H_{23}Cl_2FN_2O_3$	429/431/433 $[M+H]^+$	0.34 (A)	66 %
25		Z7b	$C_{22}H_{26}Cl_2N_2O_5$	469/471/473 $[M+H]^+$	0.30 (A)	40 %
26		Z5b	$C_{20}H_{24}Cl_2N_2O_3$	411/413/415 $[M+H]^+$	0.33 (A)	89 %
27		Lit.	$C_{21}H_{25}Cl_2N_3O_3$	438/440/442 $[M+H]^+$	0.28 (A)	52 %

28		Z23c	$C_{19}H_{23}Cl_2N_3O_4S$	460/462 [M+H]+	0.40 (A)	36 %
29		Z9c	$C_{25}H_{39}Cl_2N_3O_3$	496/498/500 [M+H]+	0.21 (A)	84 %
30		Lit.	$C_{19}H_{22}Cl_2N_2O_2$	381/383 [M+H]+	0.48 (A)	35 %
31		Lit.	$C_{20}H_{23}Cl_2N_3O_2$	408/410/412 [M+H]+	0.35 (A)	40 %

R_f value: A= (silica gel, dichloromethane / MeOH 9:1)
B= (silica gel, EtOAc)

Example 32:

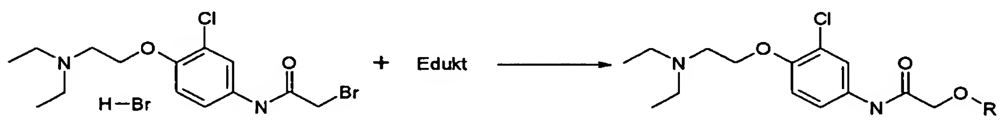


32) 2-(3-chloro-biphenyl-4-yloxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

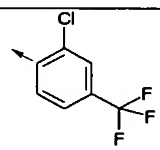
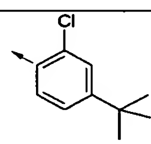
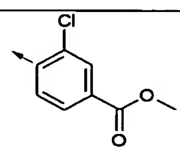
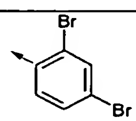
65 mg (0.47 mmol) of potassium carbonate was added to a solution of 70 mg (0.159 mmol) of 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide (intermediate product Z1c) and 64 mg (0.314 mmol) of 3-chloro-biphenyl-4-ol in 1 mL of abs. DMF and the mixture was stirred for 1 hour at 40 °C and for 15 hours at RT. The reaction mixture was diluted with dichloromethane, the org. phase was washed with sat. aqueous sodium

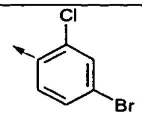
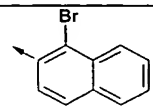
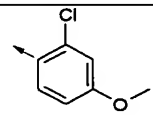
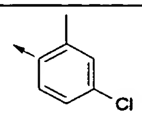
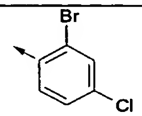
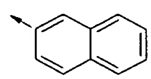
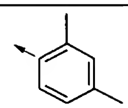
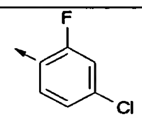
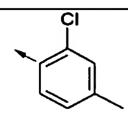
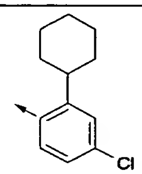
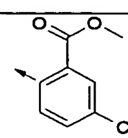
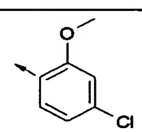
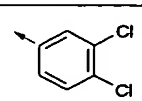
bicarbonate solution and water and dried over magnesium sulphate. Column chromatography (silica gel, dichloromethane / MeOH 9:1) yielded the product.
Yield: 51 mg (67 % of theory)
$C_{26}H_{28}Cl_2N_2O_3$ (M= 487.431)
Calc.: Molpeak$(M+H)^+$: 487/489/491
Found: Molpeak $(M+H)^+$: 487/489/491 (Cl_2)
R_f value: 0.43 (silica gel, dichloromethane / MeOH 9:1)

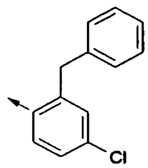
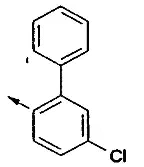
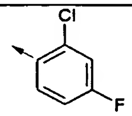
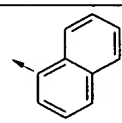
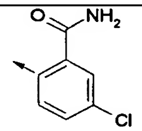
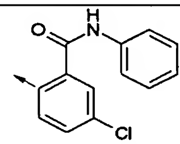
the following compounds were prepared analogously to Example 32:



while in the Table that follows the products are defined by means of the group R and the associated educts are commercially available.

Example	R	Empirical formula	Mass spectrum	R_f value	Yield (%)
33		$C_{21}H_{23}Cl_2F_3N_2O_3$	479/481/483 $[M+H]^+$	0.34 (A)	67 %
34		$C_{24}H_{32}Cl_2N_2O_3$	467/469/471 $[M+H]^+$	0.31 (A)	63 %
35		$C_{22}H_{26}Cl_2N_2O_5$	469/471/473 $[M+H]^+$	0.30 (A)	80 %
36		$C_{20}H_{23}Br_2ClN_2O_3$	533/535/537 $[M+H]^+$	0.31 (A)	82 %

37		$C_{20}H_{23}BrCl_2N_2O_3$	489/491/495/495 [M+H]$^+$	0.25 (A)	74 %
38		$C_{24}H_{26}BrClN_2O_3$	505/507/509 [M+H]$^+$	0.36 (A)	80 %
39		$C_{21}H_{26}Cl_2N_2O_4$	441/443/445 [M+H]$^+$	0.38 (A)	60 %
40		$C_{21}H_{26}Cl_2N_2O_3$	425/427/429 [M+H]$^+$	0.31 (A)	85 %
41		$C_{20}H_{23}BrCl_2N_2O_3$	489/491/493/495 [M+H]$^+$	0.32 (A)	57 %
42		$C_{24}H_{27}ClN_2O_3$	427/429 [M+H]$^+$	0.31 (A)	78 %
43		$C_{22}H_{29}ClN_2O_3$	405/407 [M+H]$^+$	0.30 (A)	73 %
44		$C_{20}H_{23}Cl_2FN_2O_3$	429/431/433 [M+H]$^+$	0.26 (A)	74 %
45		$C_{21}H_{26}Cl_2N_2O_3$	425/427/429 [M+H]$^+$	0.19 (A)	54 %
46		$C_{26}H_{34}Cl_2N_2O_3$	493/495/497 [M+H]$^+$	0.24 (A)	62 %
47		$C_{22}H_{26}Cl_2N_2O_5$	469/471/473[M+H]$^+$	0.25 (A)	68 %
48		$C_{21}H_{26}Cl_2N_2O_4$	441/443/445 [M+H]$^+$	0.31 (A)	80 %
49		$C_{20}H_{23}Cl_3N_2O_3$	445/447/449/451[M+H]$^+$	0.26(A)	66 %

50		$C_{27}H_{30}Cl_2N_2O_3$	501/503/505[M+H]+	0.36 (A)	93 %
51		$C_{26}H_{28}Cl_2N_2O_3$	487/489/491[M+H]+	0.36 (A)	83 %
52		$C_{20}H_{23}Cl_2FN_2O_3$	429/431/433[M+H]+	0.36 (A)	64 %
53		$C_{24}H_{27}ClN_2O_3$	427/429 [M+H]+	0.32 (A)	84 %
54		$C_{21}H_{25}Cl_2N_3O_4$	454/456/458[M+H]+	0.08 (A)	72 %
55		$C_{27}H_{29}Cl_2N_3O_4$	530/532/534[M+H]+	0.23 (A)	48 %

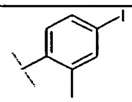
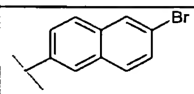
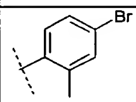
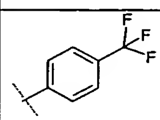
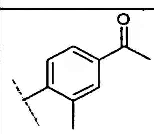
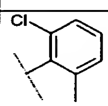
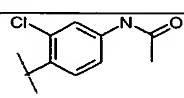
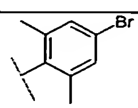
R_f value: A= (silica gel, dichloromethane / MeOH 9:1)

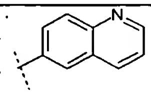
<u>General working method III (phenol alkylation I):</u>

Phenol (2.0 eq.) and potassium carbonate (3.0-5.0 eq.) are added successively to a solution of the alkyl bromide (see intermediate product Z1c) (1.0 eq.) in DMF. The mixture is stirred for 48-72 hours at RT under a nitrogen atmosphere, before being added to water. After extraction of the aqueous phase with EtOAc the organic phase is dried over magnesium sulphate. The solvent is removed using the rotary evaporator; further purification is carried out by column chromatography or crystallisation.

According to general working method III the following compounds were prepared:

while in the Table that follows the products are defined by means of the group R1 and the associated educts are commercially available.

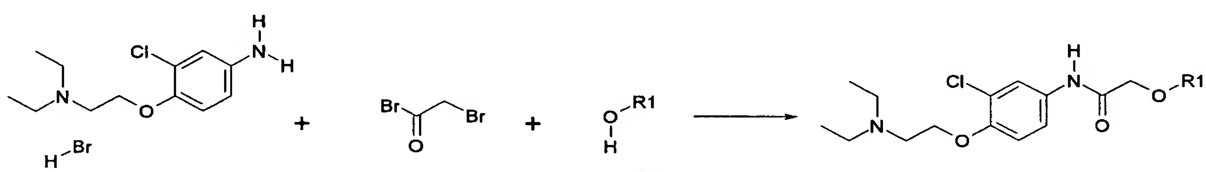
Example	R1	Empirical formula	Mass spectrum	R_f value	Yield (%)
56		$C_{21}H_{26}ClIN_2O_3$	517/519 $[M+H]^+$	0.32 (A)	47
57		$C_{24}H_{26}BrClN_2O_3$	505/507/509 $[M+H]^+$	0.42 (A)	20
58		$C_{21}H_{27}BrClN_2O_3$	469/471/473 $[M+H]^+$	0.33 (A)	49
59		$C_{21}H_{24}ClF_3N_2O_3$	445/447 $[M+H]^+$	0.32 (A)	56
60		$C_{23}H_{29}ClN_2O_4$	433/435 $[M+H]^+$	0.37 (A)	23
61		$C_{21}H_{26}Cl_2N_2O_3$	425/427/429 $[M+H]^+$	0.42 (A)	24
62		$C_{22}H_{27}Cl_2N_3O_4$	468/470/472 $[M+H]^+$	0.26 (A)	21
63		$C_{22}H_{28}BrClN_2O_3$	483/485/487 $[M+H]^+$	0.32 (A)	48

64		$C_{23}H_{26}ClN_3O_3$	428/430 [M+H]$^+$	0.23 (A)	12

Eluant: A) dichloromethane / MeOH / ammonia = 90:10:1

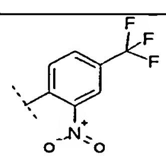
General working method IV (phenolalkylation II):

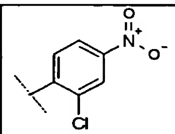
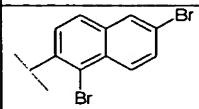
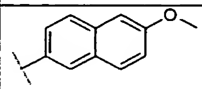
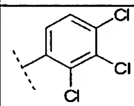
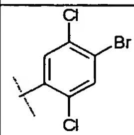
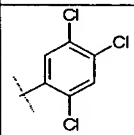
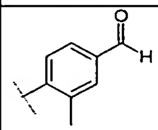
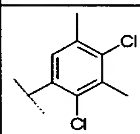
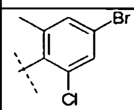
Bromoacetylbromide (1.0 eq.) in dioxane is added dropwise to a solution of the aniline (see intermediate product Z1b) (1.0 eq.) in DMF at –10°C. Then the mixture is heated to RT and phenol (1.0 eq.) in DMF and potassium-*tert*-butoxide (2.0 eq.) in *tert*-butanol are added successively. The mixture is heated to 80°C for 4 hours. DMF is eliminated in vacuo and the residue is dissolved in EtOAc. The ethyl acetate solution is washed 1x with 10 % K_2CO_3 solution, then 2x with water. The EtOAc is eliminated in vacuo. Further purification is carried out by column chromatography.
According to general working method IV the following compounds were prepared:



(Edukt)

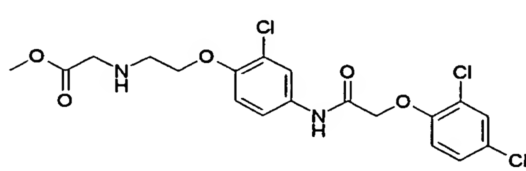
while in the Table that follows the products are defined by means of the group R1 and the associated educts are commercially available.

Example	R1	Empirical formula	Mass spectrum	R_f value	Yield (%)
65		$C_{21}H_{23}ClF_3N_3O_5$	490/492 [M+H]$^+$	0.24 (A)	6

66		$C_{20}H_{23}Cl_2N_3O_5$	456/458/460 [M+H]$^+$	0.28 (A)	7
67		$C_{24}H_{25}Br_2ClN_2O_5$	583/85/87/89 [M+H]$^+$	0.50 (A)	7
68		$C_{25}H_{29}ClN_2O_4$	455/457 [M+H]$^+$	0.24 (A)	13
69		$C_{20}H_{22}Cl_4N_2O_3$	479/81/83/85 /87 [M+H]$^+$	0.28 (A)	10
70		$C_{20}H_{22}BrCl_3N_2O_3$	521/23/25/27 [M+H]$^+$	0.28 (A)	10
71		$C_{20}H_{22}Cl_4N_2O_3$	477/79/81/83 [M+H]$^+$	0.23 (A)	8
72		$C_{22}H_{27}ClN_2O_4$	419/421 [M+H]$^+$	0.25 (A)	5
73		$C_{22}H_{27}Cl_3N_2O_3$	473/75/77/79 [M+H]$^+$	0.31 (A)	8
74		$C_{21}H_{25}BrCl_2N_2O_3$	503/05/07/09 [M+H]$^+$	0.28 (A)	8

Eluant: A) dichloromethane / MeOH / ammonia = 90:10:1

Example 75:



75) methyl (2-{2-chloro-4-[2-(2,4-dichloro-phenoxy)-acetylamino]-phenoxy}-ethylamino)-acetate

75 µL (0.54 mmol) of triethylamine and 70 mg (0.18 mmol) of N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide was added to a suspension of 45 mg (0.36 mmol) of methyl amino-acetate hydrochloride in 2 mL dichloromethane / THF (1:1). 114 mg (0.54 mmol) of sodium triacetoxyborohydride was added and the mixture was stirred for 3 hours at RT. 100 mL of 2 N aqueous sodium carbonate solution was added and the aqueous phase was exhaustively extracted with chloroform. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 71 mg (78 % of theory)

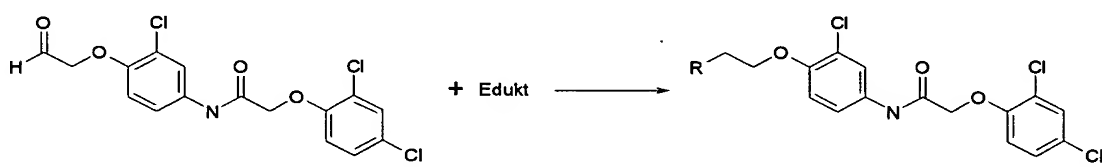
$C_{19}H_{19}Cl_3N_2O_5$ (M= 461.733)

Calc.: Molpeak$(M+H)^+$: 461/463/465/467

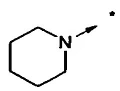
Found: Molpeak $(M+H)^+$: 461/463/465/467 (Cl_3)

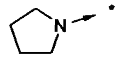
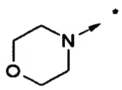
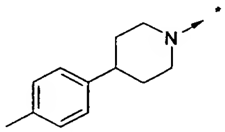
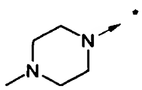
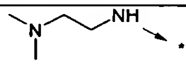
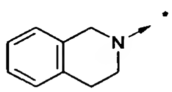
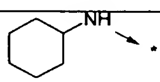
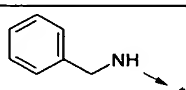
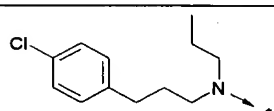
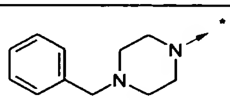
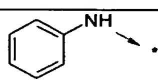
R_f value: 0.32 (silica gel, EtOAc)

The following compounds were prepared analogously to Example 75:



while in the Table that follows the products are defined by means of the group R and the associated educts are commercially available.

Example	R	Empirical formula	Mass spectrum	R_f value	Yield (%)
76		$C_{21}H_{23}Cl_3N_2O_3$	457/459/461/463 $[M+H]^+$	0.30 (A)	66 %

77		$C_{20}H_{21}Cl_3N_2O_3$	443/445/447/449 $[M+H]^+$	0.28 (A)	70 %
78		$C_{20}H_{21}Cl_3N_2O_4$	459/461/463/465 $[M+H]^+$	0.18 (B)	72 %
79		$C_{28}H_{29}Cl_3N_2O_3$	547/549/551/553 $[M+H]^+$	0.19 (B)	52 %
80		$C_{21}H_{24}Cl_3N_3O_3$	472/474/476/478 $[M+H]^+$	0.31 (A)	66 %
81		$C_{20}H_{24}Cl_3N_3O_3$	460/462/464/466 $[M+H]^+$	0.19 (A)	42 %
82		$C_{25}H_{23}Cl_3N_2O_3$	505/507/509/511 $[M+H]^+$	0.61 (B)	78 %
83		$C_{22}H_{25}Cl_3N_2O_3$	471/473/475/477 $[M+H]^+$	0.41 (B)	64 %
84		$C_{23}H_{21}Cl_3N_2O_3$	479/481/483/485 $[M+H]^+$	0.16 (B)	69 %
85		$C_{28}H_{30}Cl_3N_2O_3$	583/585/587/589 $[M+H]^+$	0.51 (B)	56 %
86		$C_{27}H_{28}Cl_3N_3O_3$	548/550/552/554 $[M+H]^+$	0.10 (B)	82 %
87		$C_{22}H_{19}Cl_3N_2O_3$	465/467/469/471 $[M+H]^+$	0.51 (C)	58 %

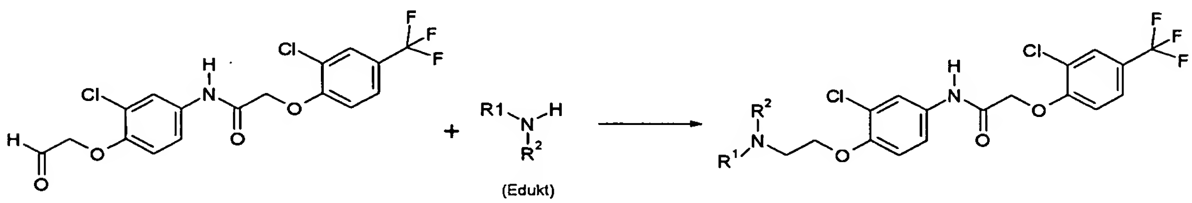
R_f value: A= (silica gel, dichloromethane / MeOH 9:1)

B= (silica gel, EtOAc)

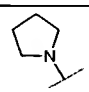
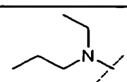
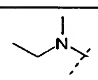
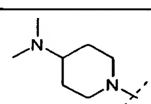
C= (silica gel, EtOAc / hexane 1:1)

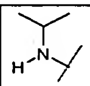
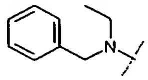
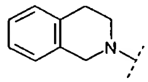
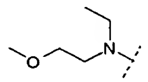
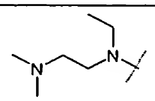
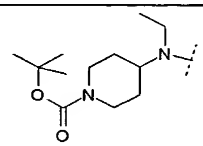
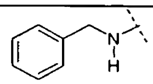
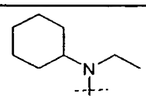
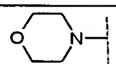
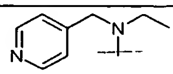
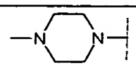
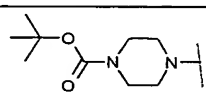
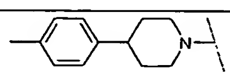
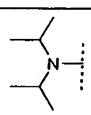
<u>General working method V (reductive amination):</u>

Conc. hydrochloric acid (2.0 eq.) is added to a solution of the aldehyde (see intermediate product Z3d) (1.0 eq.) and amine (2.0 eq.) in THF or the pH is adjusted to between 4-6 with glacial acetic acid. The mixture is stirred for 10 minutes at RT and then sodium cyanoborohydride (2.0 eq.) in THF or sodium triacetoxyborohydride (2.0 eq.) is added. The reaction mixture is stirred for 30 minutes – 24 hours at RT to 60°C, depending on the amine, before adding sat. aqueous sodium bicarbonate solution. After extraction of the aqueous phase with ether the organic phase is dried over magnesium sulphate. The solvent is removed using the rotary evaporator; further purification is carried out by column chromatography or crystallisation.
According to general working method V the following compounds were prepared:



while in the Table that follows the products are defined by means of the group R^1R^2N- and the associated educts are commercially available or known from the literature.

Example	R^1R^2N-	Empirical formula	Mass spectrum	R_f value	Yield (%)
88		$C_{21}H_{21}Cl_2F_3N_2O_3$	477/479/481 $[M+H]^+$	0.13 (A)	27
89		$C_{22}H_{25}Cl_2F_3N_2O_3$	493/495/497 $[M+H]^+$	0.26 (B)	8
90		$C_{20}H_{21}Cl_2F_3N_2O_3$	465/67/69 $[M+H]^+$	0.25 (B)	4
91		$C_{24}H_{28}Cl_2F_3N_3O_3$	534/536 $[M+H]^+$	0.10 (B)	30

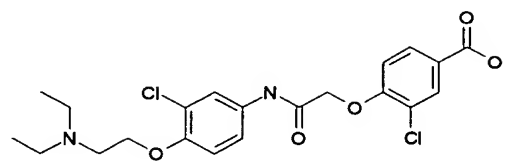
92		$C_{20}H_{21}Cl_2F_3N_2O_3$	465/467/469 [M+H]$^+$	0.28 (B)	9
93		$C_{26}H_{25}Cl_2F_3N_2O_3$	541/543/545 [M+H]$^+$	0.80 (B)	10
94		$C_{26}H_{23}Cl_2F_3N_2O_3$	539/541/543 [M+H]$^+$	0.35 (B)	19
95		$C_{22}H_{25}Cl_2F_3N_2O_4$	509/511/513 [M+H]$^+$	0.37 (B)	7
96		$C_{23}H_{28}Cl_2F_3N_3O_3$	522/524/526 [M+H]$^+$	0.18 (B)	8
97		$C_{29}H_{36}Cl_2F_3N_3O_5$	634/636/638 [M+H]$^+$	0.32 (B)	6
98		$C_{24}H_{21}Cl_2F_3N_2O_3$	513/515/517 [M+H]$^+$	0.47 (C)	27
99		$C_{25}H_{29}Cl_2F_3N_2O_3$	533/535/537 [M+H]$^+$	0.37 (C)	1
100		$C_{21}H_{21}Cl_2F_3N_2O_4$	493/495 [M+H]$^+$	0.33 (B)	13
101		$C_{25}H_{24}Cl_2F_3N_3O_3$	542/544/546 [M+H]$^+$	0.35 (B)	10
102		$C_{22}H_{24}Cl_2F_3N_3O_3$	506/508/510 [M+H]$^+$	0.15 (B)	1
103		$C_{26}H_{30}Cl_2F_3N_3O_5$	592/594/596 [M+H]$^+$	0.55 (B)	21
104		$C_{29}H_{29}Cl_2F_3N_2O_3$	581/583/585 [M+H]$^+$	0.55 (B)	18
105		$C_{23}H_{27}Cl_2F_3N_2O_3$	507/509/511 [M+H]$^+$	0.65 (B)	6

Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 95:5:0.5

B) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

C) dichloromethane / MeOH = 9:1

Example 106:



106) 3-chloro-4-{[3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy}-benzoic acid

A solution of 1.8 g (3.835 mmol) of methyl 3-chloro-4-{[3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy}-benzoate (from Example 35) and 2 ml of 2 M aqueous NaOH solution in 20 mL MeOH was refluxed for 1 hour. The reaction solution was evaporated down i. vac., diluted with water and acidified weakly with HCl. After 3 days at RT the solution was evaporated down i. vac. The residue was triturated with cold EtOH and the precipitate was filtered off.

Yield: 230 mg (13 % of theory)

$C_{21}H_{24}Cl_2N_2O_5$ (M= 455.342)

Calc.: Molpeak$(M+H)^+$: 454/456/458

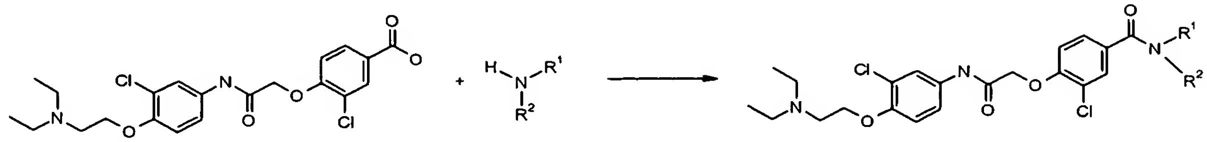
Found: Molpeak $(M+H)^+$: 454/456/458 (Cl_2)

R_f value: 0.05 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

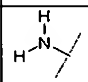
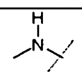
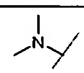
<u>General working method VI:</u>

A solution of 1.0 eq. of 3-chloro-4-{[3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy}-benzoic acid (from Example 106) and 1.07 eq. of TBTU in DMF is placed at RT. After the addition of 1.07 eq. triethylamine the mixture is stirred for 10 minutes. Then 7.0 eq. amine are added and the mixture is stirred for 16 hours at RT. The reaction mixture is combined with water or 5% sodium carbonate solution. The precipitated solid is filtered off, washed with water and dried i. vac.

According to general working method VI the following compounds were prepared:



while in the Table that follows the products are defined by means of the group R^1R^2N- and the associated educts are commercially available or known from the literature.

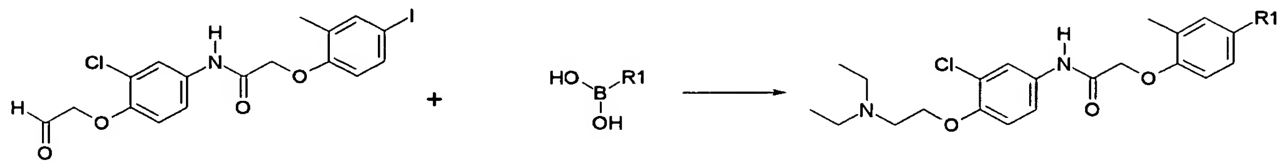
Example	R^1R^2N-	Empirical formula	Mass spectrum	R_f value	Yield (%)
107	 from $(NH_4)_2CO_3$	$C_{21}H_{25}Cl_2F_3N_3O_4$	454/456/458 $[M+H]^+$	0.37 (A)	59
108		$C_{22}H_{27}Cl_2F_3N_3O_4$	468/470/472 $[M+H]^+$	0.38 (A)	57
109		$C_{23}H_{29}Cl_2F_3N_3O_4$	482/484/486 $[M+H]^+$	0.38 (A)	55

Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

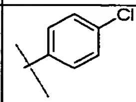
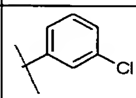
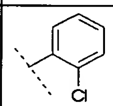
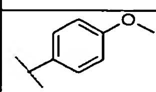
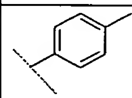
General working method VII (Suzuki coupling):

Boric acid (2.0 eq.) and tetrakis-(triphenylphosphine)-palladium (0.1 eq.) are added successively to a solution of the iodide (1.0 eq.; see Example 56) in toluene and 2M sodium carbonate solution (4.0 eq.) and stirred overnight at 80°C. The reaction solution is combined with 10 % aqueous Na_2CO_3 solution and the aqueous phase is extracted with EtOAc. The organic phases are combined and the solvent is eliminated in vacuo. Further purification is carried out by column chromatography.

According to general working method VII the following compounds were prepared:



while in the Table that follows the products are defined by means of the group R1 and the associated educts are commercially available or known from the literature.

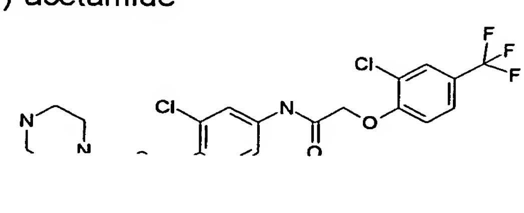
Example	R1	Empirical formula	Mass spectrum	R_f value	Yield (%)
110		$C_{27}H_{30}Cl_2N_2O_3$	501/503/505 $[M+H]^+$	0.30 (A)	4
111		$C_{27}H_{30}Cl_2N_2O_3$	501/503/505 $[M+H]^+$	0.30 (A)	4
112		$C_{27}H_{30}Cl_2N_2O_3$	501/503/505 $[M+H]^+$	0.30 (A)	6
113		$C_{28}H_{33}ClN_2O_4$	497/499/501 $[M+H]^+$	0.27 (A)	8
114		$C_{28}H_{33}ClN_2O_4$	481/483 $[M+H]^+$	0.6 (B)	21

Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

B) EtOAc / MeOH / conc. aqueous ammonia = 90:10:1

Example 115:

115) N-[3-chloro-4-(2-piperazin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



0.200 g (0.338 mmol) of *tert*.butyl 4-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-piperazin-1-carboxylate (from Example 103) were dissolved in 5.0 mL dichloromethane. After the addition of 0.5 mL (6.760 mmol) of trifluoroacetic acid the mixture was stirred for 2 hours at RT. The reaction solution was evaporated down i. vac. and the residue combined with sat. aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and evaporated down i. vac. Further purification was carried out by column chromatography.

Yield: 0.032 g (16 % of theory)

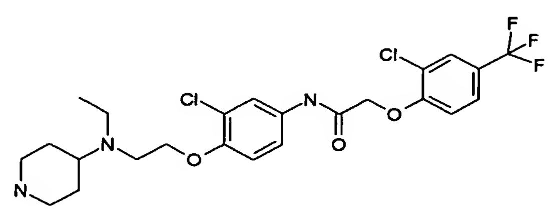
$C_{21}H_{22}Cl_2F_3N_3O_3$ * 2 CH_2O_2 (M= 584.381)

Calc.: Molpeak$(M+H)^+$: 492/494/496 (Cl_2)

Found: Molpeak $(M+H)^+$: 492/494/496 (Cl_2)

R_f value: 0.22 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 116:



116) N-{3-chloro-4-[2-(ethyl-piperidin-4-yl-amino)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

0.180 g (0.284 mmol) of *tert*.butyl 4-[(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-ethyl-amino]-piperidine-1-carboxylate (from Example 97) were dissolved in 5.0 mL dichloromethane. After the addition of 0.44 mL (5.680 mmol) of trifluoroacetic acid the mixture was stirred for 2 hours at RT. The reaction solution was evaporated down i. vac. and the residue combined with sat. aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and evaporated down i. vac. Further purification was carried out by column chromatography.

Yield: 0.011 g (6 % of theory)

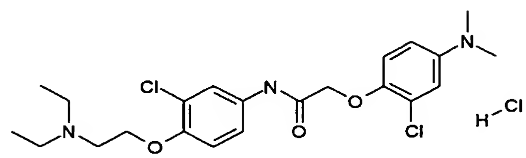
$C_{24}H_{28}Cl_2F_3N_3O_3$ * 2 CH_2O_2 (M= 626.462)

Calc.: Molpeak$(M+H)^+$: 534/536/538 (Cl_2)

Found: Molpeak $(M+H)^+$: 534/536/538 (Cl_2)

R_f value: 0.25 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 117:



117) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-dimethylamino-phenoxy)-acetamide

94.7 mg (0.200 mmol) of 2-(4-amino-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide (from Example 118), 0.149 mL (37%, 2.000 mmol) of formaldehyde solution and 62.8 mg (1.000 mmol) of sodium cyanoborohydride was placed in 5.0 mL acetonitrile at RT. The pH was adjusted to 4-5 with glacial acetic acid with stirring. After 1 hour the reaction mixture was acidified with 12 % HCl and stirred for 10 minutes. Then it was made slightly alkaline with 20 % potassium carbonate solution. The aqueous phase was extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and evaporated down i. vac. The residue was purified by column chromatography (silica gel; EtOAc / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95). The oily residue was combined with ethereal HCl, evaporated down i. vac. and dissolved in 10 mL isopropanol. The precipitate formed was filtered off and dried i. vac.

Yield: 0.035 g (36 % of theory)

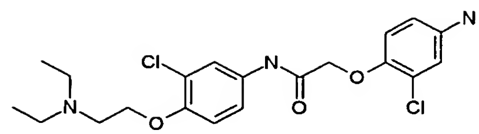
$C_{22}H_{29}Cl_2N_3O_3$ * HCl (M= 490.862)

Calc.: Molpeak$(M+H)^+$: 454/456/458 (Cl_2)

Found: Molpeak $(M+H)^+$: 454/456/458 (Cl_2)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Example 118:



118) 2-(4-amino-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

0.310 g (0.679 mmol) of N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-nitro-phenoxy)-acetamide (from Example 66) was dissolved in 10.0 mL of EtOAc. After the addition of 0.030 g Pt/C (5%) the mixture was hydrogenated at RT under 15 psi H_2 atmosphere for 5 hours. The reaction mixture was filtered and the filtrate was evaporated down i. vac. The residue was dissolved with a little EtOH. The precipitate formed was filtered off and dried i. vac.

Yield: 0.050 g (17 % of theory)

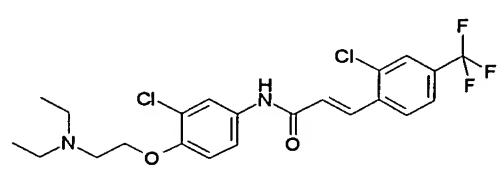
$C_{20}H_{25}Cl_2N_3O_3$ (M= 426.347)

Calc.: Molpeak$(M+H)^+$: 426/428/430 (Cl_2)

Found: Molpeak $(M+H)^+$: 426/428/430 (Cl_2)

R_f value: 0.24 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 119:



119) (E)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

0.29 mL (2.10 mmol) of triethylamine was added to a solution of 0.28 g (1.00 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine-hydrochloride

(intermediate product Z1b), 0.25 g (1.00 mmol) of (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid and 0.34 g (1.05 mmol) of TBTU in 10 mL abs. THF and the mixture was stirred for 1 hour at RT. The reaction mixture was evaporated down i. vac. and the residue was combined with dichloromethane and water. The org. phase was separated off, washed with sat. aqueous sodium bicarbonate solution and water and evaporated down i. vac. The residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

Yield: 150 mg (32 % of theory)

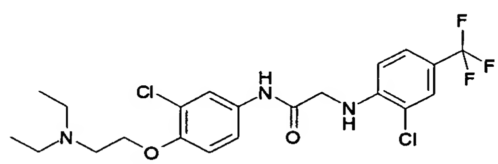
$C_{22}H_{23}Cl_2F_3N_2O_2$ (M= 475.342)

Calc.: Molpeak$(M+H)^+$: 475/477/479

Found: Molpeak $(M+H)^+$: 475/477/479 (Cl_2)

R_f value: 0.2 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 95:5:1)

Example 120:



120) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenylamino)-acetamide

A solution of 0.228 g (0.511 mmol) of 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide (intermediate product Z1c) and 0.200 g (1.023 mmol) of 2-chloro-4-trifluoromethyl-phenylamine in 5 mL DMF was stirred for 16 hours at 90 °C and then for 24 hours at 120 °C. The reaction mixture was cooled to RT, diluted with water and exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The residue was dissolved in DMF and purified by HPLC-MS (Stable Bond C18; 3.5 □m; water:acetonitrile:formic acid 9:1:0.01 → 1:9:0.01 over 9 min).

Yield: 11 mg (5 % of theory)

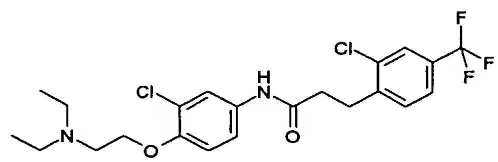
$C_{21}H_{24}Cl_2F_3N_3O_2$ (M= 478.346)

Calc.: Molpeak$(M+H)^+$: 478/480/482

Found: Molpeak $(M+H)^+$: 478/480/482 (Cl_2)

R_f value: 0.24 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 121:



121a) 3-(2-chloro-4-trifluoromethyl-phenyl)-propionic acid

2.00 g (7.981 mmol) of (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid was added at RT to a suspension of 0.500 g Raney nickel in abs. MeOH and the mixture was hydrogenated for 4 hours at 50 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

Yield: 1.90 g (94 % of theory)

$C_{10}H_8ClF_3O_2$ (M= 252.622)

Calc.: Molpeak$(M-H)^-$: 251/253

Found: Molpeak $(M+H)^+$: 251/253 (Cl)

121b) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-propionamide

The product was obtained analogously to Example 119 starting from 0.400 g (1.433 mmol) of) 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine-hydrochloride (intermediate product Z1b) and 0.362 g (1.433 mmol) of 3-(2-chloro-4-trifluoromethyl-phenyl)-propionic acid.

Yield: 340 mg (50% of theory)

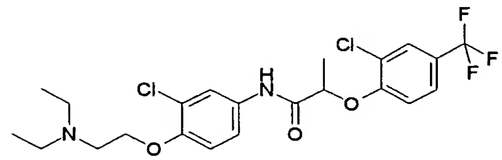
$C_{22}H_{25}Cl_2F_3N_2O_2$ (M= 477.358)

Calc.: Molpeak$(M-H)^-$: 477/479/481

Found: Molpeak $(M+H)^+$: 477/479/481 (Cl_2)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Example 122:



122a) ethyl 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionate
10.00 g (50.87 mmol) of 2-chloro-4-trifluoromethyl-phenol, 7.11 mL (55.00 mmol) of ethyl 2-bromopropionate and 7.60 g (55 mmol) of potassium carbonate in 100 mL DMF was stirred for 16 hours at 50 °C and then filtered. The filtrate was evaporated down i. vac., combined with water and exhaustively extracted with EtOAc. The combined org. extracts were washed with 10% aqueous sodium carbonate solution and water, dried over sodium sulphate and evaporated down i. vac.
Yield: 14.10 g (93 % of theory)
$C_{12}H_{12}ClF_3O_3$ (M= 296.676)
Calc.: Molpeak$(M+Na)^+$: 319/321
Found: Molpeak $(M+Na)^+$: 319/321 (Cl)
R_f value: 0.6 (silica gel, EtOAc / petroleum ether 4:1)

122b) 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionic acid
50 mL (0.100 mol) of 2 M aqueous NaOH solution was added to a solution of 14.00 g (0.047 mol) of ethyl 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionate in 100 mL EtOH and the mixture was refluxed for 1 hour. EtOH was evaporated off i. vac., the residue was diluted with ice water and acidified with 2 M aqueous HCl. The precipitate formed was filtered off, washed with water and dried at 70 °C i. vac.
Yield: 12.10 g (96 % of theory)
$C_{10}H_8ClF_3O_3$ (M= 268.622)
Calc.: Molpeak$(M-H)^-$: 267/269

Found: Molpeak $(M-H)^-$: 267/269 (Cl)

122c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-propionamide-hydrochloride

0.342 mL (2.000 mmol) of ethyl-diisopropylamine was added to a solution of 0.364 g (1.500 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (intermediate product Z1b), 0.403 g (1.500 mmol) of 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionic acid and 0.562 g (1.750 mmol) of TBTU in 10 mL abs. THF and the mixture was stirred for 1 hour at RT. The reaction mixture was evaporated down i. vac. and the residue combined with dichloromethane and water. The org. phase was separated off, washed with sat. aqueous sodium bicarbonate solution and water and evaporated down i. vac. The residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

Yield: 450 mg (57 % of theory)

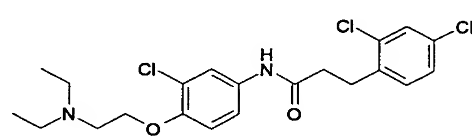
$C_{22}H_{25}Cl_2F_3N_2O_3$ * HCl (M= 529.818)

Calc.: Molpeak$(M+H)^+$: 493/495/497

Found: Molpeak $(M+H)^+$: 493/495/497 (Cl_2)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 95:5:0.5).

Example 123:



123) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2,4-dichloro-phenyl)-propionamide

A solution of 0.271 g (1.236 mmol) of (3-(2,4-dichloro-phenyl)-propionic acid in 3.00 mL thionyl chloride was stirred for 2 hours at RT, evaporated down i. vac. and dissolved in 10 mL dichloromethane. This solution of the acid chloride was slowly added dropwise, while cooling with ice, to a solution of 0.300 (1.236 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine

(intermediate product Z1b) and 0.32 mL (1.854 mmol) of ethyl-diisopropylamine in 10 mL dichloromethane and the mixture was stirred for 16 hours at RT. The reaction mixture was washed with sat. aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated down i. vac. The residue was dissolved in EtOAc and purified by column chromatography (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1).

Yield: 60 mg (11 % of theory)

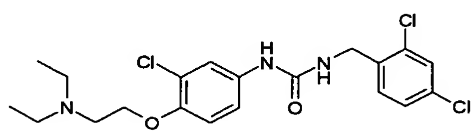
$C_{21}H_{25}Cl_3N_2O_2$ (M= 443.)

Calc.: Molpeak(M-Na)$^-$: 441/443/445

Found: Molpeak (M-Na)$^-$: 441/443/445 (Cl_2)

R_f value: 0.27 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Example 124:



124) 1-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2,4-dichloro-benzyl)-urea

203 mg (1.236 mmol) of CDT in 4 mL DMF was added to a solution of 345 mg (1.236 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine-hydrochloride (intermediate product Z1b) and 0.56 mL (4.000 mmol) of triethylamine in 40 mL THF and the mixture was stirred for 2 hours at RT. 176 mg (1.236 mmol) of 2,4-dichloro-benzylamine was added, the reaction mixture was refluxed for 4 hours and then evaporated down i. vac. The residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 80:20:1) and the product was triturated with diisopropylether.

Yield: 300 mg (55 % of theory)

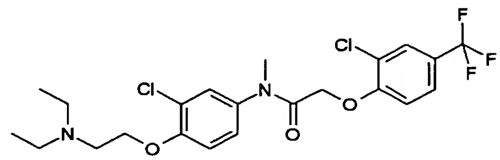
$C_{20}H_{24}Cl_3N_3O_2$ (M= 444.792)

Calc.: Molpeak$(M+H)^+$: 444/446/448

Found: Molpeak $(M+H)^+$: 444/446/448 (Cl_3)

R_f value: 0.73 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 80:20:1)

Example 125:



125a) tert.butyl [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbaminate

0.31 mL (2.266 mmol) of triethylamine was added to a solution of 0.500 g (2.06 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine and 0.495 g (2.266 mmol) of Boc-anhydride in 10 mL dichloromethane at RT and the mixture was stirred for 48 hours. The reaction mixture was diluted with dichloromethane and the org. phase was washed with sat. aqueous sodium bicarbonate solution. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. Column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1) yielded the product.

Yield: 500 mg (71 % of theory)

$C_{17}H_{27}ClN_2O_3$ (M= 342.869)

Calc.: Molpeak$(M+H^+$: 343/345

Found: Molpeak $(M+H)^+$: 343/345 (Cl)

125b) [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine

Under a nitrogen atmosphere a solution of 500 mg (1.458 mmol) of tert.butyl [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbaminate in 10 mL THF was slowly added dropwise to a suspension of 165 mg (4.374 mmol) of lithium aluminium hydride in 20 mL abs. THF and the mixture was stirred for 16 hours at RT. 165 µL of water, 165 µL of 15% aqueous NaOH solution and a further 495 µL water was added and the precipitate formed was filtered off. The

filtrate was dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1).

Yield: 180 mg (48 % of theory)

$C_{13}H_{21}ClN_2O$ (M= 256.778)

Calc.: Molpeak$(M+H)^+$: 257/259

Found: Molpeak $(M+H)^+$: 257/259 (Cl)

R_f value: 0.61 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1)

125c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-N-methyl-acetamide

293 mg (0.911 mmol) of TBTU and 123 mg (0.911 mmol) of HOBT in 5 mL were added to a suspension of 231 mg (0.911 mmol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (intermediate product Z2b) in 5 mL abs. THF and the mixture was stirred for 10 minutes at RT. 180 mg (0.701 mmol) of [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine and 0.18 mL (1.051 mmol) of ethyl-diisopropylamine were added, the mixture was stirred for 16 hours at RT and evaporated down i. vac. The residue was purified by column chromatography (silica gel, silica gel, dichloromethane / MeOH / conc. aqueous ammonia 85:15:1).

Yield: 150 mg (43 % of theory)

$C_{22}H_{25}Cl_2F_3N_2O_3$ (M= 493.357)

Calc.: Molpeak$(M+H)^+$: 493/495/497

Found: Molpeak $(M+H)^+$: 493/495/497 (Cl_2)

R_f value: 0.416 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Some test methods for determining an MCH-receptor antagonistic activity will now be described. In addition, other test methods known to the skilled man are used, e.g. by inhibiting the MCH-receptor-mediated inhibition of cAMP production, as described by Hoogduijn M et al. in "Melanin-concentrating hormone and its receptor are expressed and functional in human skin", Biochem. Biophys. Res Commun. 296 (2002) 698-701 and by biosensory measurement of the binding of MCH to the MCH receptor in the presence of antagonistic substances by plasmon resonance, as described by Karlsson OP and Lofas S. in "Flow-Mediated On-Surface Reconstitution of G-Protein Coupled Receptors for Applications in Surface Plasmon Resonance Biosensors", Anal. Biochem. 300 (2002), 132-138. Other methods of testing antagonistic activity to MCH receptors are contained in the references and patent documents mentioned hereinbefore, and the description of the test methods used is hereby incorporated in this application.

MCH-1 receptor binding test

Method:	MCH binding to hMCH-1R transfected cells
Species:	Human
Test cell:	hMCH-1R stably transfected into CHO/Galpha16 cells
Results:	IC50 values

Membranes from CHO/Galpha16 cells stably transfected with human hMCH-1R are resuspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer (50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/ml aprotinin, 1 µg/ml leupeptin and 1 µM phosphoramidone) to a concentration of 5 to 15 µg/ml. 200 microlitres of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of ^{125}I-tyrosyl melanin concentrating hormone (^{125}I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 microlitres. After the incubation the reaction is filtered using a cell harvester through 0.5% PEI treated glass fibre filters (GF/B, Unifilter Packard). The membrane-bound radioactivity retained on the filter is then determined after the addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard).

The non-specific binding is defined as bound radioactivity in the presence of 1 micromolar MCH during the incubation period.

The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site.
Standard:
Non-labelled MCH competes with labelled ^{125}I-MCH for the receptor binding with an IC50 value of between 0.06 and 0.15 nM.
The KD value of the radioligand is 0.156 nM.

MCH-1 receptor-coupled Ca^{2+} mobilisation test

Method:	Calcium mobilisation test with human MCH (FLIPR^{384})
Species:	Human
Test cells:	CHO/ Galpha 16 cells stably transfected with hMCH-R1
Results:	1st measurement: % stimulation of the reference (MCH 10^{-6}M) 2nd measurement: pKB value

Reagents:	HBSS (10x)	(GIBCO)
	HEPES buffer (1M)	(GIBCO)
	Pluronic F-127	(Molecular Probes)
	Fluo-4	(Molecular Probes)
	Probenecid	(Sigma)
	MCH	(Bachem)
	bovine serum albumin (protease-free)	(Serva)
	DMSO	(Serva)
	Ham's F12	(BioWhittaker)
	FCS	(BioWhittaker)
	L-Glutamine	(GIBCO)
	Hygromycin B	(GIBCO)
	PENStrep	(BioWhittaker)
	Zeocin	(Invitrogen)

Clonal CHO/Galpha16 hMCH-R1 cells are cultivated in Ham's F12 cell culture medium (with L-glutamine; BioWhittaker; Cat.No.: BE12-615F). This contains per 500 ml 10% FCS, 1% PENStrep, 5 ml L-glutamine (200 mM stock solution), 3 ml hygromycin B (50 mg/ml in PBS) and 1.25 ml zeocin (100 µg/ml stock solution). One day before the experiment the cells are plated on a 384-well microtitre plate (black-walled with a transparent base, made by Costar) in a density of 2500 cells per cavity and cultivated in the above medium overnight at 37°C, 5% CO_2 and 95% relative humidity. On the day of the experiment the cells are incubated with cell culture medium to which 2 mM Fluo-4 and 4.6 mM Probenicid have been added, at 37°C for 45 minutes. After charging with fluorescent dye the cells are washed four times with Hanks buffer solution (1 x HBSS, 20 mM HEPES), which is combined with 0.07% Probenicid. The test substances are diluted in Hanks buffer solution, combined with 2.5% DMSO. The background fluorescence of non-stimulated cells is measured in the presence of substance in the 384-well microtitre plate five minutes after the last washing step in the FLIPR^{384} apparatus (Molecular Devices; excitation wavelength: 488 nm; emission wavelength: bandpass 510 to 570 nm). To stimulate the cells MCH is diluted in Hanks buffer with 0.1% BSA, pipetted into the 384-well cell culture plate 35 minutes after the last washing step and the MCH-stimulated fluorescence is then measured in the FLIPR^{384} apparatus.

Data analysis:

1st measurement: The cellular Ca^{2+} mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10^{-6}M). This measurement serves to identify any possible agonistic effect of a test substance.

2nd measurement: The cellular Ca^{2+} mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10^{-6}M, signal is standardised to 100%). The EC50 values of the MCH dosage activity curve with and without test substance (defined concentration) are determined

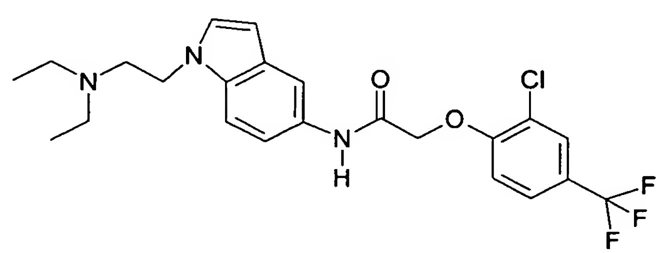
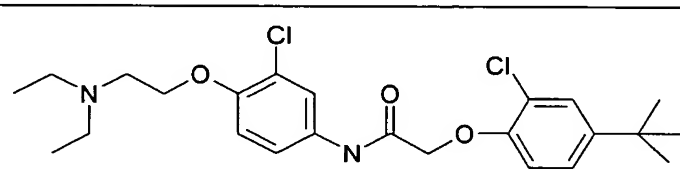
graphically by the GraphPad Prism 2.01 curve program. MCH antagonists cause the MCH stimulation curve to shift to the right in the graph plotted.

The inhibition is expressed as a pKB value:

$pKB=\log(EC_{50(testsubstance+MCH)} / EC_{50(MCH)} -1) -\log c_{(testsubstance)}$

The compounds according to the invention, including their salts, exhibit an MCH-receptor antagonistic activity in the tests mentioned above. Using the MCH-1 receptor binding test described above an antagonistic activity is obtained in a dosage range from about 10^{-10} to 10^{-5} M, particularly from 10^{-9} to 10^{-6} M.

The following IC50 values were determined using the MCH-1 receptor binding test described above:

Compound according to Example no.	Structure	IC50 value
12		41 nM
34		17 nM

Some examples of formulations will be described hereinafter, wherein the term "active substance" denotes one or more compounds according to the invention, including their salts. In the case of one of the combinations with one or more active substances described, the term "active substance" also includes the additional active substances.

Example A

Capsules for powder inhalation containing 1 mg active substance

Composition:

1 capsule for powder inhalation contains:

active substance	1.0 mg
lactose	20.0 mg
hard gelatine capsules	50.0 mg
	71.0 mg

Method of preparation:

The active substance is ground to the particle size required for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

Example B

Inhalable solution for Respimat® containing 1 mg active substance

Composition:

1 spray contains:

active substance	1.0 mg
benzalkonium chloride	0.002 mg
disodium edetate	0.0075 mg
purified water ad	15.0 µl

Method of preparation:

The active substance and benzalkonium chloride are dissolved in water and packed into Respimat® cartridges.

Example C

Inhalable solution for nebulisers containing 1 mg active substance

Composition:

1 vial contains:

active substance	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

Method of preparation:

The active substance, sodium chloride and benzalkonium chloride are dissolved in water.

Example D

Propellant type metered dose aerosol containing 1 mg active substance

Composition:

1 spray contains:

active substance	1.0 mg
lecithin	0.1 %
propellant gas ad	50.0 µl

Method of preparation:

The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised contained with a metering valve.

Example E

Nasal spray containing 1 mg active substance

Composition:

active substance	1.0 mg
sodium chloride	0.9 mg
benzalkonium chloride	0.025 mg
disodium edetate	0.05 mg
purified water ad	0.1 ml

Method of preparation:

The active substance and the excipients are dissolved in water and transferred into a corresponding container.

Example F

Injectable solution containing 5 mg of active substance per 5 ml

Composition:

active substance	5 mg
glucose	250 mg
human serum albumin	10 mg
glycofurol	250 mg
water for injections ad	5 ml

Preparation:

Glycofurol and glucose are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

Example G

Injectable solution containing 100 mg of active substance per 20 ml

Composition:

active substance	100 mg
monopotassium dihydrogen phosphate $= KH_2PO_4$	12 mg
disodium hydrogen phosphate $= Na_2HPO_4 \cdot 2H_2O$	2 mg
sodium chloride	180 mg
human serum albumin	50 mg
Polysorbate 80	20 mg
water for injections ad	20 ml

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules.

Example H

Lyophilisate containing 10 mg of active substance

Composition:

Active substance	10 mg
Mannitol	300 mg
human serum albumin	20 mg

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into vials; freeze-dried.

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20 mg
mannitol	200 mg
water for injections ad	10 ml

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (WfI); transferred into ampoules.

Example I

Tablets containing 20 mg of active substance

Composition:

active substance	20 mg
lactose	120 mg
maize starch	40 mg
magnesium stearate	2 mg
Povidone K 25	18 mg

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

Example J

Capsules containing 20 mg active substance

Composition:

active substance	20 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example K

Suppositories containing 50 mg of active substance

Composition:

active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example L

Injectable solution containing 10 mg of active substance per 1 ml

Composition:

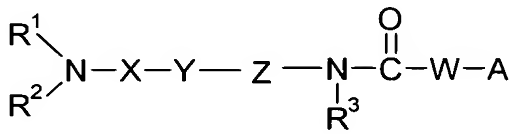
active substance	10 mg
mannitol	50 mg
human serum albumin	10 mg
water for injections ad	1 ml

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

Abstract

The present invention relates to amide compounds of general formula I



I

wherein the groups and residues A, W, X, Y, Z, R^1, R^2 and R^3 have the meanings given in claim 1. The invention further relates to pharmaceutical compositions containing at least one amide according to the invention. In view of their MCH-receptor antagonistic activity the pharmaceutical compositions according to the invention are suitable for the treatment of metabolic disorders and/or eating disorders, particularly obesity, bulimia, anorexia, hyperphagia and diabetes.